Photoadaptation of the skin during exposure to narrowband ultraviolet b radiation

Layton, Susan

Susan Layton. Photoadaptation of the Skin during Exposure to Narrowband Ultraviolet B Radiation.
Thesis submitted for the degree of Master of Science at The University of Durham, School of Biological Sciences.
2000

The aim of this study is to determine the rate at which UVB radiation takes effect in order to produce an effective regimen for treatment.

Psoriasis, a chronic, proliferative, inflammatory disease that is under genetic and environmental control is the major condition where UVB radiation successfully reduces symptoms.

The treatment regimen for at present involves exposure doses that are increased alogarithmically and is based upon previous broadband knowledge. No established protocol for TL01 UVB phototherapy exists.

Patients were randomly chosen from Dryburn Hospital Phototherapy Department. Baseline minimal erythemal measurements were calculated (MED_0) and random measurements were taken during the course using a single TL01 lamp. Data was collected over a period of 1 year and the effects of photoadaptation were determined. Factors considered include the period of time in between treatments, the number of treatments already attended and cumulative doses.

MED ratios were calculated and analysed to produce a skin adaptation model. The majority of patients were phototested 2-6 times during the treatment course, which lasted 6 weeks (mean). Results indicated that missing a treatment session was insignificant to the rate of tolerance.

The model for tolerance was calculated to be:

$$T_n = 1 + 3\,[1 - \exp(-0.03n)] \qquad n = \textit{tolerance following n treatments}$$

A revised protocol was established and a clinical trial implemented. Protocol results indicated that the new regimen significantly reduced cases of burning and significantly reduced the cumulative doses of radiation. Revised protocol patients (yellow group) received total doses of 12.7 J/cm^2 (median) and the original regimen provided a total of 16.9 J/cm^2 (median). There was no significance in the time length of the treatment protocols.

The revised protocol is therefore significantly more suitable because it reduces chances of excessive erythema discomfort and by reducing the radiation exposure doses the regimen also reduces the risk of skin malignancies.

Photoadaptation of the skin during exposure to narrowband ultraviolet B radiation

by

Susan Layton

Thesis submitted for the degree of

Master of Science

at

The University of Durham

School of Biological Sciences

2000

CONTENTS

FIGURES & TABLES

DECLARATION

No material contained within this thesis has previously been submitted in part or whole for a degree in this or any other university.

All information derived from the work of others which is contained within the thesis has been acknowledged.

All research material described in the thesis was original at the time of data collection and was performed solely by the author.

The copyright of this thesis rests with the author.

No quotations from it should be made without their prior written consent and information derived from it should be acknowledged.

For my family

Acknowledgements

Many thanks to Dr FA Ive and Dr MM Carr for financial support to allow me to complete my thesis.

Appreciation to Professor BL Diffey and Dr C Jahoda for support and guidance.

Thank-you to nurses and Sister Marsh of the PUVA Department.

Special thanks to Dr MC Steele for her continuous interest, advice and support.

1 INTRODUCTION

1.1 Anatomy and Physiology of the Skin.

Changes that occur in the skin as the result of treatment can only be understood if the physiology and anatomy of the skin are known.

The normal epidermis is a terminally differentiated squamous epithelium, 95% of the cells being keratinocytes, which become pigmented through the donation of melanin from melanocytes. The epidermis can be divided into 4 distinct regions based upon the morphology of the cell.

stratum basale or stratum germinativum (basal cell layer)
stratum spinulosum (spinous/prickle cell layer)
stratum granulosum (granular cell layer)
stratum corneum (keratin cell layer

The stratum basale tends to be only 1 cell thick but in glabrous or hyperproliferated dermis the thickness may increase to 2-3 cells, all of which are capable of cellular proliferation. These small columnar cells (10-14nm) contain many ribosomes, an elongated nucleus and dense tonofilament bundles, indicating very high levels of protein synthesis. As the cells move from the dermis towards the surface they alter in morphology and function. At the stratum spinosum the cells flatten and the nucleus becomes condensed. The cytoplasm contains less RNA and the cells begin to become keratinized. The cells contain numerous desmasomal connection plaques or prickles that allow stable connections throughout the layer and they are capable of mitotic division as demonstrated during proliferative and malignant conditions. At the granular layer the nucleus becomes lost and organelles become lysed in an organised fashion. Once the cells reach the granular layer masses of granular shaped keratohyalin granules can be seen, arranged in rows within the cytoplasm. The stratum spinosum and the granular layer also contain laminated vesicles (100-300nm). These granules become important in the stratum corneum for cellular

adhesion and barrier functions because their lipid contents are released into the intracellular space. Stratum corneum cells (corneocytes) are keratinized by the release of keratin from the granules under the influence of filaggrin. Filaggrin has been shown by histochemical and biochemical studies to be a basic protein rich in histadine and lacking in sulphur (Reaven et al 1965). Profilaggrin, a high molecular weight phosphorilated protein is contained in the keratohyalin granules and upon release is converted to its aggregate form by specific phosphatases. Filaggrin interacts with keratin causing filament formation, which is reproducible in vitro (Dale et al 1978). Keratin is a multistranded α helix stabilised by disulphide bonds of cysteine sulphydryl groups, hydrogen bonds and Van der Waal forces. Filaggrin is degraded as the cells move towards the stratum corneum and the amino acid products are involved in skin water retention.

Corneocyte membranes develop membrane-associated proteins, which are insoluble, and cross-linked (Simon et al 1987). Involucrin (95kDa) is the soluble precursor, assembled by the action of epidermal transglutaminases e.g. glutamyl lysine. If involucrin is labelled, cell differentiation rates can be measured and analysis of diseases such as psoriasis can be examined (Dover et al 1987).Other proteins have also been found to associate with the keratinocyte membrane. These include loricrin, which is a 70% glycine and serine, and 8% cysteine protein. At the stratum granulosum level the loricrin granules can be seen by immunogold labelling and they reach the cell periphery by the stratum corneum stage. A 210kDa and 95kDa protein have also been isolated and these combine with non-specific proteins to form the insoluble cornified envelope. At this stage in the cell differentiation process, desmosomal connections also become degenerated. These symmetrical junctions have a core of 30nm and are composed of cadherin proteins; desmoplanktin I (250kDa), desmoplanktin II (220kDa), desmocalnin (240kDa), desmoplakin III (83kDa) and desmoplakin IV, depending on the epithelial type (Ebling et al 1992).

The horny or keratin layer is the first line of defence and forms a durable barrier, which maintains the water content of the skin at 10-20%. The keratinised dead cells are continuously being sloughed off and lubricated by cellular transpiration and sebaceous and sweat secretions. It is thought that the presence of a granular layer is necessary for a significant keratinisation and it is only in the presence of hair follicles that a true granular layer is formed. In glabrous skin the keratin is thick and is found to be associated with sweat glands rather than hair follicles (Ebling et al 1992).

There are also many other types of cells in the epidermis and the dermis which have specialised functions. There is an intricate blood vessel system in the dermis supplying nutrients, oxygen and other essential products to the skin and removing any waste products. The blood vessels are also involved in supplying a rich number of white blood cells to the dermis and epidermis, e.g. neutrophils, monocytes and lymphocytes, which prevent infection of foreign substances through phagocytosis, interleukin production (released by neutrophils to raise body temperature and stimulates the liver to uptake iron and therefore reduce the availability of iron for bacterial cell division)and interferon release (released by some cells in response to viral attack and interferes with the replication of viral DNA and RNA). Specific lymphocytes and complement proteins are also made available so that cell mediated and humoral immune responses can occur. Among other effects this stimulates the production of antibodies by lymphocytes , which in turn have a number of effects, such as opsonisation (the binding of micro-organisms and stimulation of complement), lysin production (stimulation of the lysis of micro-organisms), agglutination of microbes and neutralisation of toxins e.g. diphtheria or tetanus. Memory T cells are also available, stored in the lymph nodes, in order to allow a rapid response to any subsequent invasion from antigens. In the dermis there are complex supporting apparatus consisting of elastic and collagen fibres. It is in-between these fibres that the macrophages, lymphocytes and fibroblasts of the dermis are contained.

Mast cells can be isolated from tissue in the upper dermis and stimulation leads to exocytosis if histamine granules. Histamine causes inflammation, increasing the blood supply to the tissue and therefore increasing the number of white blood cells in the area in order to fight off infection. Somatosensory neurones, hair follicles and glands are also abundant in the dermis. The glands include sweat glands, sebaceous glands, tear glands and mammary glands. The gland cells move up into the epidermis and onto the surface of the skin where they secrete their products. They have their own stem cells and patterns of cell renewal. The somatosensory neurones include various sized neurones with different nerve endings that are involved in sensing such as pain, flutter, warm or cold stimuli. The nerves take the stimuli to the brain stem, spinal cord, thalamus and cerebral cortex and it is the nerve endings that respond to the different stimuli e.g. mechanoreceptors such as the raffini corpuscle, the pacinion corpuscle or the meissners corpuscle, nocireceptors which have bear endings that respond to pain and thermoreceptors which respond to warmth and cold (Berne & Levy 1990).

1.2 The Aetiology of Psoriasis.

The actual cellular mechanisms that lead to psoriasis are complicated and not fully understood. T cells are known to play an important role in inflammation and cell growth through the release of particular cytokines that act directly and indirectly upon keratinocytes. If we look at the histology of psoriasis, the cells in the germnative layer are twice as thick as normal and the cell cycle is altered in length. Normally the epidermis maintains a constant thickness because of the balance between cell division and cell loss. Various factors work in collaboration to maintain this equilibrium. Cell growth stimulants and inhibitors are particularly important. Stimulants include epidermal growth factors, proteins that stimulate keratinocyte division directly, transforming growth factor that acts upon the keratinocyte in an autocrine manner, basic fibroblast growth factors, platelet derived growth factors and insulin like growth factors. Inhibitors are termed chalones and are produced by suprabasal cells. By acting directly at the stratum basale level they increase the turnover time of the keratinocyte. The

exact point of inhibition is unknown and chalones include transforming growth factor β, pentapeptide (glut-asp-ser-gly-ala), α and β interferons and tumour necrosis factor. In psoriasis the balance between cell growth and cell loss is disturbed and the subsequent plaques are formed. Keratinocytes, T cells, dermal, epidermal, antigen presenting cells, macrophages, polymorphonucleocytes, mast cells, endothelial cells fibroblasts, smooth muscle cells and nerves are all implicated in this condition. They are thought to act together in an integral and complex manner but the actual mechanisms are unknown.

In conditions such as psoriasis the keratin layer becomes disrupted. The water balance of the skin is altered and the skin becomes reduced in its ability to function as a protective barrier. Psoriasis is a common chronic, proliferative, inflammatory disease, which is under genetic and environmental control.

Genetic Factors

Psoriasis is well established as being under genetic control and various genes are known to be involved in its expression. The major locus that has been isolated is the HLA gene cluster. Epidemiological surveys of populations indicate that psoriasis affects 1.5-3% Western Europe and Scandinavian populations. It is due to epidermal hyperproliferation, inflammation and vascular changes in the skin. Watson et al in 1972 performed surveys that showed 46% of relatives and 1.2% spouses of psoriatic patients also present the condition.16% of children had psoriasis when 1 parent had the condition and only 7.8% when neither parent was inflicted. Both TNFα and □β genes have been identified in the HLA gene cluster, the HLA cluster being found on chromosome 6 position 21.3. There are a variety of functions carried out by these molecules including stimulation of the expression genes for other cytokines, their receptors and transcription factors. TNFα, like IL1 induces ICAM, MCAF and IL8 and is thought to be primarily produced by the cytokine as well as by macrophages and other cells. TNFα's bioactivity is increased in psoriatic keratinocytes and leads to the stimulation of hyperplasia. Recent evidence produced by Tomfohrde et al in 1994 also indicates there may be

genes on the distal long arm of chromosome 17. With the human genome project underway a world wide search for the function of all genes is in process, so hopefully in the near future the genetic control of psoriasis and many other conditions will be better understood.

Environmental Factors

There are many environmental factors that influence this condition. They exert their effects through biological means. Some of these conditions are described briefly below:

1.2.1Skin trauma

In those who suffer from psoriasis it has been well observed that skin trauma takes a lot longer to heal (up to 3 times the recovery length) and scarring is much more commonplace. Also at the site of an injury psoriatic plaques may develop. Such injuries include physical, chemical or electrical trauma, surgery scars, infective and inflammatory damage. The reaction tends to occur 7-14 days after the incident and may lead to spreading of the disease to a wider area of the body. The reaction is all or none and because the psoriasis is capable of spreading, humoral factors are thought to be involved (Eyre et al 1984).

1.2.2 Infection

In 1964 Whyte et al demonstrated that streptococcal infection plays an important role in the stimulation of psoriasis and administration of antibiotics e.g. erythromycin/penicillin and rifampicin leads to a significant psoriatic improvement in many patients (Rosenberg et al 1986). It is thought that the streptococcal infection produces a major immune response that leads to increased levels of white blood cells in the skin, particularly neutrophils (confirmed through biopsies). The most common psoriasis produced in this way is guttate but other forms may also be worsened through infection. Removal of the tonsils in prone children may also prevent recurrence (Whyte 1964).

1.2.3 Endocrine Factors

Reports have shown that during hormonal changes e.g. puberty and menopause, psoriatic exacerbation increases (Ingram 1954).In a study performed on pregnant patients, 40% showed improvement, and 15% worsened during pregnancy. After birth 50% degenerated and 10% of the patient's skin condition improved. High doses of oestrogen may also exacerbate this condition by unknown mechanisms (Ebling 1992, Dunna 1989).

1.2.4 Metabolic Factors

Diabetes mellitus patients often find that prolonged or recurrent hypoglycaemia may flare psoriasis. Psoriatic patients who are unable to control their blood sugar levels effectively are therefore much more likely to express the disease than those who are capable of blood sugar maintenance. Diabetics have higher levels of glucose in the tissue than normal and regular deviations in concentration will lead to metabolic alterations and increased cell turn over rates (Hunter 1995).

1.2.5 Sunlight

Although for the majority of patients sunlight helps their skin, evidence suggests that about 5% of patients are worsened by sunlight and have more severe psoriasis during the summer months. 40% of these patients are diagnosed as polymorphic light eruption patients and psoriasis is classed as a secondary condition. The people who suffer most from this problem tend to be the elderly, females and those with skin type 1(never burn always tan) (Ebling 1992, Ros et al 1987).

1.2.6 Drugs

Beta Blockers. Both β_1 and β_2 adrenergic receptor blockers may lead to certain skin conditions erupting e.g. lichenoids, eczema and psoriasis. Eruption normally occurs approximately 5 days after the drug is administered and is due to keratinocytes possessing β_2 receptors on their cell surface. Inhibition of stimulation in this way leads to reduced [cAMP]i and [Ca++]i. Reduction of

these intracellular messengers stimulates an increase in cellular proliferation and reduces cell differentiation. β blockers are given for conditions such as angina arrhythmia, hypertension, postmyocardial infarction, migraines, essential tremors and thyrotoxicosis (Abel et al 1986).

Lithium Carbonate Normally administered as a prophylactic to sufferers of psychotic depression, lithium carbonate reduces the intracellular sodium concentration though displacement. Reduced sodium levels leads to reduced intracellular cAMP and lowering of the cAMP levels are interpreted by the cell to increase cell proliferation and reduce cell differentiation. Lithium carbonate also increases the number of polymorphonuclearcytes in epidermal and dermal circulation, it increases their motility and their phagocytotic activity and this too leads to hyperproliferation (Barth et al 1986).

Antimalarial Drugs In 1950-60 it came to light that antimalarial drugs e.g. quineurine, chloroquine and hydroxychloroquine aggravate psoriasis. Research into the mechanisms of aggravation have failed to produce a valid answer but anti-inflammatory mechanisms and immunosuppressive effects have been reported in vitro with chloroquine (Ebling 1992).

1.2.7 Psychogenic Factors

There is an established connection between the emotional state of the patient and the severity of the psoriasis. Psychological stress may lead to exacerbation of the condition but the state of the patient may lead to a reduced ability to cope with or administer their treatment. It could therefore be a more indirect mechanism of aggravation than a direct one (Baughman 1971). In 1940-1970s experiments involved epidemiological studies and Farber et al (1968) found 40% psoriatic patients expressed the condition during times of stress. Other studies related the appearance of psoriasis to major incidents e.g. illness, sexual assault or death (Gatson 1987). The most recent studies accept psoriasis is affected by stress and have attempted to define the connection in physiological terms. The body responds to stress by stimulating the adrenal gland, anterior pituitary and the cerebral cortex. Stimulation reduces

lymphocytic, neutrophilic and natural killer cell activity. It increases adrenaline release, blood glucose levels and may lower serum cortisol levels leading to a flare in psoriasis (Duller 1986). There is also evidence that the nervous system can be an influence, releasing local neuropeptides e.g. substance P which acts on mast cells to initiate inflammation (Ginsburg 1995).

1.2.8 Alcohol

It appears that alcohol may lead to an increase in the severity of psoriasis. Studies have found that psoriatic patients drink more than the average person and Gupta et al (1993) found alcohol abuse reduces the effectiveness of particular therapies including UVB light therapy, dithranol and steroid treatment. Alcohol breaks down in the body to form toxins that are concentrated in the blood. The skin becomes flushed during alcohol consumption and this aggravates the inflamed psoriatic lesions. In the long term, the calories in alcohol may lead to overweight problems and the increased body folds are prone to sweating and flaring of psoriasis. Alcohol also leads to reduced zinc concentrations which is necessary for skin healing and excessive drinking may lead to liver damage which increases the side effects of prescribed drugs e.g. methotrexate. The side effects include haematological, hepatic and gastrointestinal toxicity (Monk et al 1986).

1.2.9 Cigarette smoking

For those patients who smoke there appears to be a dose responsive relationship between the number of cigarettes smoked and the development of psoriasis. The numbers could correspond to the amount of stress in the person's lifestyle and therefore be related to psychological factors rather than the direct effect of the tobacco smoke. Smoking reduces the effectiveness of the immune system and can often lead to throat infections that trigger psoriasis. The chemicals that are contained in the tobacco also interfere with the healing responses of the skin (Dave 1997).

1.2.10 Acquired Immunodeficiency Syndrome (AIDS)

Studies have demonstrated that there is a significant relationship between AIDS and psoriasis. Some patients experience psoriasis for the first time after contracting the HIV virus whilst others experience extreme flaring of the condition. The effect that AIDS has upon psoriatic skin is unknown but because treatment normally involves immunosupressive drugs, treatment can be difficult. Psoriasis appears to be greatly improved by the administration of cyclosporin which inhibits T helper cells function (Ebling 1992) and a recent study involving acitretin found that the administration of this drug is effective and safe. The adverse effects are also tolerable e.g. pruritus, hair loss, dry skin and cheicitus (Buchheri et al 1997).

1.3 The immunology of psoriasis

UVB was originally thought to act directly upon the keratinocyte but further evidence suggests direct action upon the immune system and inflammatory cells. Examination of psoriatic plaques confirms the presence of several cytokines e.g. interleukin 1, 2, 6 (IL1, IL2, IL6), chemokine, IL8, MGSA/gro, TNFα and several growth factors including insulin-like and EGF-like growth factors Bos et al 1988).

I shall now describe some of the different cytokines and their role in the biochemical alterations that occur during psoriasis.

1.3.1 IL1,2,3,4,5 and CSFs

Normal skin contains high levels of IL1. Psoriatic activity increases IL1 mRNA and intracellular protein concentrations. IL1 receptors are also increased, particularly in the basal layer. IL2 levels become raised in psoriatic plaques and experiments show exogenous introduction of IL2 leads to plaque formation. Studies have not, however, found increased bioactivity of IL2. Mature T cells produce IL4 and IL5 and mast cells are able to release IL3, 4,5 and GMCSF and experiments involving cultured keratinocytes have found that IL3 or a

similar molecule is produced by these cells. It is highly likely that all these molecules are present in psoriatic plaques but whether they are produced by keratinocytes or other cells are not known. They are thought to play a major role in cutaneous inflammation and stimulating the survival and function of Langerhans cells (Lee et al 1988).

1.3.2 IL6

IL6 has many functions in the body, one of which is as an autocrine mitogen in psoriatic epidermis. IL6 mRNA is not raised in lesions but reports have found increased activity at plaque margins. T cells have been shown to induce IL6 production in cultured keratinocytes and it primarily activates B cells. The actual functional role of IL6 is debatable may be involved in hyperplasia and inflammation (Hunter 1995).

1.3.3 Interferons

INF-like antiviral activity is increased in psoriatic lesions, being due to INFα in the basal layer and dermal cells and INFγ in the stratum corneum, mononuclear cells and endothelial cells. Intradermal injection of INFγ leads to psoriatic lesion production in susceptible patients and increases in 'normal' individuals INFγ is suggested to act directly on keratinocytes to produce hyperplasia (Nickoloff 1988).

1.3.4 Chemokines

IL8 and gro peptides are known to be active in psoriasis. mDNA for these molecules are in very high levels in keratinocytes and are very bioactive. Their function is not fully understood (Hunter 1995).

1.3.5 Growth Factors

Many EGF-like growth factors are over expressed in psoriatic lesions and evidence indicates that they act in an autocrine manner to cause hyperplasia in the lesional area and the surrounding skin. Inflammatory cells are also thought to be stimulated by EGF- like growth factors (Nanney et al 1986). Insulin-like

growth factors are found in raised concentrations in the basal and suprabasal layer of psoriatic lesions and in vitro experiments indicate they act directly upon keratinocytes to stimulate growth. However, it is not known if psoriatic keratinocytes express insulin-like growth factors. Fibroblast growth factors (FGFs) have been reported in large concentrations in psoriatic plaques and are involved in wound healing. By acting in a paracrine manner on keratinocytes and are probably involved in the inflammation and blood supply of the lesions. Platlet derived growth factors (PDGFs) stimulate connective tissue production but they do not stimulate keratinocytes in vitro. Receptors are found, however on cells in the papillary dermis where they may stimulate dermal cells to release other keratinocyte mitogens (Bauer 1986).

1.3.6 Neuropeptides

NGF, prolactin and vasoactive intestinal peptide (VIP) are 3 neuropeptides that potently stimulate in vitro keratinocyte growth. NGF binds to high and low affinity receptors and acts autocrinely but it has never been isolated in psoriatic plaques. Prolactin is highly mitogenic for keratinocytes but there is no evidence of its expression during this condition. VIP is found widely in the central and peripheral nervous system and increases 6 fold in psoriatic lesions. Studies have found that cytokines produce their effects by acting through multiple pathways. But in psoriasis they are thought to have effect by increasing intracellular concentrations of cAMP (Halprin 1975, Marcelo et al 1979). It is thought that immunological alterations that occur in psoriasis actually increase the cAMP concentrations. The increased cAMP levels induce gene transduction and cell growth and lead to the production of the characteristic red, raised lesions. cAMP exerts its effects through activation of cAMP-dependent protein kinases (cAMPPKs). There are 3 known mammalian cAMPPKs that effect cell growth and abnormal cAMPPK type 2 is thought to be responsible for psoriatic hyperplasia (Tounier et al 1995).

Therefore the expression of psoriasis and its effects upon the skin are very complex. Many inflammatory and immune cells play important roles in the stimulation of this condition and many chemicals interact to produce the typical

symptoms of psoriasis. The major effect of these chemicals is to produce inflammation, increase cell growth and stimulate an immune response. The biochemicals are thought to exert their effects through raising cAMP levels and many experiments have involved immunosuppressants in order to determine the role of cAMP. In 1996 Ockenfels et al used cyclosporin A and FK 506 to inhibit secretion of T cell cytokines and cAMP levels were measured prior to and during incubation. The study found that the keratinocyte proliferation rate is decreased by the introduction of cyclosporin A and FK 506 due to a reduction in cAMP formation and the consequence is suppression of psoriasis. cAMP activates intracellular pathways that lead to cell proliferation. FK506 reduces intracellular cAMP and therefore plaque formation.

1.4 Ultraviolet Radiation Physics

The electromagnetic spectrum ranges from radiowaves through to X rays and gamma rays. The optical radiation part of the spectrum can be split up into the component wavelengths by passage through a prism but it was not until 1802 that Johann Retter discovered radiation beyond the visible spectrum, which is now termed ultraviolet. Ultraviolet radiation is classified as the region from 400nm to 100nm and can be further subdivided into 3 groups, although the divisions of these wavelengths are variable to some degree:

UVA 400-320nm

UVB 320-290nm

UVC 290-200nm

Ultraviolet radiation is emitted spontaneously by the sun and stars and can be artificially produced for irradiation by, for example, gas discharge lamps such as the low pressure mercury arc lamp (Diffey 1982).

1.4.1 Ultraviolet Radiation Sources

The most effective wavelengths for phototherapy of psoriasis range from 295-320nm and modern lamps reflect this. Of all ultraviolet radiation, UVB (290-320nm) has the most therapeutic effect upon psoriasis and UVC (200-290nm) produces erythema but with no therapeutic effect (Anderson et al 1984). For many years there were no specific lamps available and lamps designed for other purposes were used. Today, there is a choice of specialist lamp systems available, produced by several manufacturers. In 1974 the Task Force on Photobiology reviewed PUVA and UVB equipment (Harber et al 1974). In 1981 Horwitz and Frost expressed the significance of uniform light distribution during treatment with fluorescent bulbs. They reported that fluorescent tubes do not have a constant output along their length, the output being greatest in the centre. The trunk is more sensitive to UV than the lower limbs so lesions in this area (ie trunk) clear more effectively. They concluded that tubes should be arranged to accommodate this but the problem is overcome in our department through standing the patient on a stool to raise the legs 10cm from the floor.

1.4.2 Phototherapy Equipment

There are several types of equipment available and ultraviolet lamps can be classified into 2 groups according to the mechanism of ultraviolet production:

Medium/high pressure mercury arc lamp

Ultraviolet radiation (UVR) is produced when an electrical current is passed through a gas (vaporised mercury). The mercury atoms collide with the electrodes and they move to a higher transitional state. On returning to the resting state the atoms release the excess energy as UV, visible and infrared radiation. The wavelengths and intensities of the radiation depend upon the pressure in the lamp and the addition of a metal halide e.g. lead iodide or iron iodide alter the spectrum emitted so that appropriate spatial emission is enhanced. A glass filter can also be fitted in front of the lamp to reduce the emission of wavelengths below 290nm. The trouble with this, however, is that the glass filter alters its transmission depending upon the temperature and the lamp must reach thermal equilibrium (approx. 20 minutes) before the patient

can be exposed to the light. Examples of arc lamps are the Alpine sunlamp and Hohensonne lamp. The arc lamps are stacked in vertical columns of usually 5 lamps/column and 2-4 columns are arranged to provide uniform irradiance during treatment.

Fluorescent lamps

This is a mercury vapour lamp that is coated with phosphor. The mercury, at low vapour pressure, emits radiation at the wavelength of 253.7nm The phosphor coated glass envelope absorbs the radiation and re-emits it by the process of fluorescence at either visible, UVA or UVB wavelengths, depending upon the chemical nature of the phosphor. Examples of UVB fluorescent lamps are Philips TL01 (narrow band), Philips TL12 (broad band), Sylvania UV12 (broad band), and Sylvania UV6 (broad band). The fluorescent cubicles incorporate up to 48 lamps, 2m in length mounted in a cabinet that encloses around the patient or a bed that houses 28 lamps arranged in an anterior and posterior canopy.

UVB cabinets come in two forms, those that feature a built in fully electronic measuring and dosing meter and those that have a timing control only. For the timed cabinets extra equipment is necessary to calibrate the machine and ensure the lamps output, so that accurate treatments can be administered. This is done using hand held radiometers. The output of the lamps depends upon the amount of usage, the temperature, the warm up time and mains voltage. When high and medium mercury pressure lamps are switched on there is an excess of liquid mercury in the lamps and it takes several minutes for thermal equilibrium to be reached and the mercury to vaporise. Once the tubes are switched off they can not be restarted for 30 minutes and therefore the machines remain switched on throughout the clinic. Fluorescent lamps may be switched on and off without any problem but work most efficiently at 25°C, establishing a steady output after 1 minute. As temperature increases the output from the tubes decreases so fans are incorporated into the machines to maintain temperature. New lamps exhibit a running in time. That is when the lamps are first switched on they produce a high output which quickly

deteriorates to a steady output at an equilibrium. For fluorescent lamps this period lasts 100 hours and for mercury arc lamps it takes only 20 hours. As the usage progresses the radiance from the lamps gradually decreases. Both the cabinets with built in sensors and those without possess pros and cons. With the cabinets that do not have built in radiometers, training of personnel and the frequent reading of the irradiance is time consuming and there is always a danger of the radiometer malfunctioning or giving inaccurate readings due to incorrect calibration or the sensor being covered during reading. The relationship between prescribed dose, measured irradiance and exposure time is:

Exposure time (minutes) = [1000 x Prescribed dose (J/cm^2)] / [60 x Irradiance (mW/cm^2)]

If the sensor is built into the cabinet it must be cleaned at regular intervals to ensure dust does not build up in front of the detector leading to lowered readings and an increased risk of burning patients. As previously described the lamps do not emit uniformly along their length and the detectors only sense light from one area. This could lead to false readings, however, because the sensors always read the same area of the tube. Patients must also be warned that they must not touch the sensors or obstruct them in any way because this will lead to increased exposure time and burning. This is always a potential problem in these cabinets because once the patient is inside the cabinet their activities are unknown. It must also be remembered that the sensors, like the UV tubes deteriorate in time. This too could lead to problems if not realised. For these reasons I believe the timed cabinets to be safer and more reliable. There are also cabinets available that possess both UVB and UVA tubes. These cabinets are convenient in that they enable a choice of spectrum to be available for patients and they take up less space than 2 separate cabinets. But the lamps are more widely spaced than the separate machines and the dangers of administering the wrong waveband of UVR could have serious adverse effects.

1.4.3 PUVA Equipment

PUVA equipment has been available for approximately 20 years in Britain and like UVB cabinets they contain fluorescent tubes. PUVA lamps emit at 315-400 nm, peaking at 352nm (Diffey & McKinlay. 1983). Like UVB there are a variety of machines available, ranging from whole body to extremities units and the lamps are almost always used in conjunction with psoralen tablets as photochemotherapy. Psoralen is normally administrated in the form of tablets but may also be given in cream, gel or lotion form or put into a bath. The lotions only become particularly useful if the extremities are being treated because it means the patients do not have to ingest the psoralen which makes their eyes sensitive to UVA and may make them feel nauseous. The starting doses for PUVA have been revised over the years and it is now recommended to use 0.25-4.0 J/cm2 depending upon the skin type. However the validity of skin typing is now debatable and it is possible that UVB sensitivity is not as skin type related as was once thought (Rampen et al 1988, Cox et al 1989).

1.5 Ultraviolet Effects on Normal Skin

UVB produces hyperplasia, tanning, oedema, sunburn cell induction, itching, cis uronic acid (cis UCA) formation, immune responses and inflammation.

1.5.1 Hyperplasia and Tanning

These are important protective mechanisms that prevent further penetration of UV radiation. Tanning reduces the risk of developing basal and squamous cell carcinoma and people with a lower potential for tanning are more at risk of skin carcinoma. Tanning is due to melanocytes producing melanin in melanosomes. The melanosomes move through the cell dendrites and transfer the melanin into neighbouring keratinocytes. The transferred melanin forms a protective layer over the outer aspect of the keratinocyte nucleus and protects against UVR (mainly 290-320nm) by acting as an energy sink and free radical scavenger. Melanin is produced in 2 forms:

eumelanin (the most common form, black-brown in colour)
phaemelanin (the less common form, yellow or red in colour)

1.5.2 Oedema

A protective mechanism brought about by excessive UVR. Langerhan cells, dendritic antigen presenting cells, are thought to be the initial immunological line of defence. They engulf antigens, transport them to lymph nodes and present them to the T lymphocytes. Psoriasis is thought to stimulate Langeran cell production and treatment with UVR reduces numbers and 20-40% lose their dendritic capability. Broad band UVB has been shown to reduce dendritic cell accumulation 48 hours after irradiation. Some experiments suggest TNF-α and dendritic cells are not produced by narrow band UVB.

1.5.3 Erythema/Sunburn Reaction

Painful erythema is more likely with UVB than PUVA. For UVB the maximum erythema occurs 8-24 hours after administration and for PUVA maximum erythema is at 72-96 hours. Erythema is due to increased blood flow in the sub papillary of the dermis and begins to occur 1-4 hours after exposure. The erythema is caused by cellular damage through photochemical reactions which leads to vasodilatation. If erythema is severe DNA may become damaged and inflammatory mechanisms become initiated. Inflammation also causes vasodilatation and oedema may occur due to the release of epidermal hydrolases. Mitosis becomes inhibited for 24-36 hours, after which a massive stimulation occurs that decreases after a few days. Epidermal thickening, by up to 50-60%, is due to an increase in the number of proliferating basal cells and hypergranulosis and hyperkeratosis results. Increased numbers of melanocytes are also present in the epidermis (Marks 1996).

Mild burning is normally treated with moisturising cream, analgesics and topical steroids. Paste bandages may be used for severe burning/blistering.

1.5.4 Itching

This is a common problem and reduced with emollient application. Antihistamines may be prescribed for severe cases to reduce the inflammation.

1.5.5 Cold sores (herpes simplex)

This virus may be stimulated by UVB radiation in some patients who already harbour the virus and the usual applications of topical treatment is employed. The more severe, long-term side effects of phototherapy include chronic actinic damage, dyskeratosis, skin cancers, immunological alterations, photoageing and cataract formation. For these reasons phototherapy departments administer the minimum UVR dose possible to each patient and cover body parts that do not need treating e.g. using a visor, wearing a T shirt or being fully clothed if only the face is being treated. I now intend to describe photoageing and cancer risks in more detail.

1.5.6 Photoageing

Long term administration of UVR has been found to lead to thinning of the skin and premature ageing. Ageing can be defined as a reduction in the functional capacity of the skin and can be classified into two categories.

- intrinsic ageing which occurs in all skin and is only slightly altered in appearance.
- premature ageing which leads to rough, wrinkled skin that may be irregularly pigmented and have undergone elastosis, lacking in tensile strength and possess solar comedones and actinic keratoses. Ageing occurs at the cellular level and can be characterised according to the skin typing.

<u>Types 1 & 2</u>

Freckling

Telanglectasia and /or fine wrinkles

focal diffuse anthropy with irregular depigmentation

Actinic keratoses and /or irregular hyperpigmentation

<u>Types 3, 4 & 5</u>

diffuse hyperpigmentation

lentigines
elastosis with coarse/shallow skin
severe elastosis with deep furrows.

Elderly peoples' skin cells are less efficient at perceiving and responding to extracellular signals due to reduced receptors and signal transduction pathway levels. When UVR causes DNA damage, the cell differentiation process is thought to be reduced in functional ability and evidence suggests that melanocytes become altered in density during photoaging. UVR also leads to the formation of irregularly pigmented areas e.g. ephilides (which are brown/yellow in appearance and macular), actinic lentigines (an area where keratinocytes and melanocytes are damaged and the epidermis is hyperpigmented due to an increase in the number of melanocytes and the histology of the skin is altered. They possess great potential to becoming malignant) Lentigo maligna (lesions which are brown/black/white and slowly increase in size with a great risk of developing into malignant melanoma) and hypomelanoses (which are due to the epidermis becoming reduced or lacking in melanocytes) (Ortonne 1996).

After long periods of ultraviolet exposure the elastic tissue becomes damaged by a process known as elastosis. There are two views as to how this occurs. In 1992 Shafetter-Kochanek claimed UVR exposure leads to the release of growth factors from the damaged epidermal cells and these chemicals stimulate fibroblasts to release elastic tissue elements that are constructed in an abnormal and rapid manner. Braverman (1982) proposed the other alternative which is that the normal collagen is degraded and replaced with abnormal elastin. The damaged skin tissue is unable to support the peripheral blood vessels and passive dilation occurs which is seen as a flushed appearance in the patient. I consider this view to be more realistic, based on my own knowledge that similar abnormalities can be seen in autoimmune diseases such as osteoarthritis which is due to degradation of hyaline cartilage through the action of antibodies. The elastic collagen fibres become replaced with nonelastic fibrous collagen which is ineffective as a shock absorbing

cartilage (J.P.Pearson, unpublished data).Cartilage like skin, is composed of a basic matrix of collagen. Collagen is a triple helix polypeptide, assembled as procollagen molecules which become chemically linked in the fibroblastic cell's cytoplasm. It is then released by exocytosis into the extracellular fluid where it becomes assembled into a complex interlocking matrix. Within the matrix is a ground substance. The ground substance of skin is composed of glycosaminoglycans and that of cartilage is protein and glycosaminoglycans. The molecules are covalently and noncovalently bound to form proteoglycans. Each proteoglycan contains 50-100 side chains of glycosaminoglycans which have large numbers of hydrophilic carboxyl and sulphate groups attached and because of this over 60% of the net weight of the cartilage is water.

The collagen and ground substance of both the skin and cartilage provide tensile strength, resilience to stress and pressure and to absorb forces applied to the surface.

There are three types of cartilage found at the end of the bones, walls of the trachea, in the larynx and nasal septum.

1) hyaline cartilage – very hydrophilic, 70-80% water, very elastic, spongy and mouldable. Found at ends of long bone.
2) Fibrous cartilage – consists of thick bundles of collagen and acts as ashock absorber in the tendons, ligaments, symphysis pubis and inbetween the vertebrae.
3) Yellow cartilage – consists of a dense network of collagen fibres with flexibility and strength.Found in the external pinna, epiglottis and eustachian tube .

If hyaline cartilage becomes damaged eg. through antibody attack or through traumatic damage there are two processes by which repair occurs.

1) Intrinsic repair – Where the damaged tissue and chondrocytes are replicated and the matrix is repaired.
2) Extrinsic repair – where severe damage causes mass degradation and the cells proliferate and produce fibrocartilage and cartilage. The repaired

cartilage is more fibrous than the original tissue and less efficient at weight baring which can lead to more structural damage. This is very similar to the degradation process described by Braverman in 1982 and because of the similarities in chemical composition between skin and cartilage, I suspect it to be most probable (Hughes et al 1987).

1.5.7 Skin Cancer

Skin cancers include melanoma, basal cell carcinoma and squamous cell carcinoma. UV damages the DNA of cells, particularly the pyramidine dimer and repair is normally 99.99% successful, however, if the damage is not repaired tumour promotion may occur. The carcinogenic effects of UVA and psoralen have been known for many years and in 1979 Tam et al produced evidence to link psoriatic PUVA patients and skin cancer. Psoralen itself has not been found to be carcinogenic but a study performed in 1982 suggests 8-methoxypsoralen may cause cancer to the kidneys, lungs and subcutaneous tissue in rats (National Institute of Health). The doses administered however were up to 75 times greater than those given to humans so the significance of this study is disputable. UVB has been established as carcinogenic in humans for decades but several studies have shown UVB to be relatively safe. (Grupper et al 1980, Larko et al 1982). Stern et al (1980) examined cases of psoriatic cancer patients and found that patients exposed to 300 treatments or more have a 4.7 times greater risk of developing cancer than those who have had little or no UVB treatment.

It has been suggested that been reported to lead to increased reports of genital tumours in men. Stern et al in 1990 found the risk of squamous cell carcinoma in those receiving PUVA/UVB treatment the incidence of cancer can be reduced depending upon the protocol of UV administration (Henseler et al 1981). In 1979 Stern et al published the results of an extensive study that suggested PUVA may promote basal cell carcinoma and squamous cell carcinoma in patients who are genetically predisposition or at risk from other factors, rather than being a carcinogen in its own right. Young reviewed the carcinogenic effects in 1990 and found that because psoralen binds reversibly

to DNA causing unstable crosslinks, it is therefore highly mutogenic and potentially carcinogenic. PUVA has also to be 96 times more likely to develop genital tumours than the general population. The risk is dose dependent and it is therefore common practice to cover the genitals during therapeutic treatment.

The group also compared the protocols for PUVA administration in Europe to America. In comparison to Europe, Americans administer PUVA over longer periods of time at lower doses. Studies comparing cancer prevalence between these 2 places indicate the American regime to be more carcinogenic. Such comparisons can be problematic because geographical location, genetic predisposition, prior exposures to carcinogens, prior histories of carcinomas, and skin types are confounding factors.

The adverse effects of phototherapy are minimised by undertaking several preliminary precautions. The patients who are selected must not be at high risk from developing cancers. Such patients include those with a history of skin cancer, previous arsenic treatment, those previously exposed to ionising radiation and those who have been previously prescribed antimetabolites e.g. hydroxyurea, cyclosporin A and methotrexate. However, administration is obviously at the doctor's discretion. Through the administration of drugs e.g. retinoids a lower dose of radiation can be given which could be beneficial to many patients who may be receiving high cumulative doses. The safety threshold for photochemotherapy (PUVA) is 200 treatments or 1200 J/cm^2. Yearly examination of patients skin is a sound idea and patients should be told to avoid the sun when ever possible. During PUVA treatment protective glasses should be worn for 24 hours to reduce the risk of cataract formation. The use of sunscreen and clothing to areas that are not necessary to be treated is also sensible.

1.6 The Effects Of Ultraviolet Radiation On Psoriatic Skin

Psoriasis stimulates the production and circulation of cytotoxic lymphocytes, particularly natural killer cells (NKCs), and T cells e.g. CD56+, CD16+, CD2+, CD116+, CD3- and CD 25+ and CD3+, respectively. The main function of

these cells is to protect against foreign bodies and to reduce tumour cell formation. UVR probably exerts its effects by reducing epidermal T cells and NKC function.

The effects of UVB upon T cells was studied in 1995 by Kreuger et al using a protocol similar to the Goekerman regime. (A regimen that involved the application of crude coal tar to the skin and then exposing the patient to UV radiation.) In all 9 cases the psoriasis became exacerbated ($P<0.001$). The psoriatic plaques reduced in thickness by 43-80% ($P<0.001$) and keratinocytes proliferation decreased by 69% ($p<0.001$). Biochemical analysis of the lesions found that α_3 integrin, which is expressed basally and suprabasally, becomes predominantly basal following phototherapy and T cells also become significantly reduced. CD8+ lymphocytes decrease in the epidermal-dermal interface and upper papillary dermis and CD3+ cells reduce by 70-100%. CD1+ lymphocytes, however, appear to actually increase in the epidermal psoriatic lesions.

Psoriatic keratinocytes produce HLA-DR and ICAM-1. Analysis of these proteins during psoriasis exacerbation found that there is little or no expression of these molecules following phototherapy treatment. The effects of therapy upon T cells are thought to be selective to the affected areas and repeated exposure does not reduce the number of cells further. The effect upon NKCs was studied by Gilmour in 1993. The study involved 20 patients with chronic plaque psoriasis and 3 with guttate psoriasis. In comparison to 11 normal patients there was no significant increase in NKC activity but after 4 weeks of TL01 treatment activity was significantly decreased and began to increase after treatment had discontinued. After 4 weeks of stopping treatment the activity level still had not reached the original level. The group suggested that NKC inhibition is dose and wavelength dependent and mechanisms of control are unknown but may be due to:

- direct action on the cells as they circulate in dermal capillaries leading to functional damage

- UVR stimulates the release of a soluble mediator which enters circulation and effects NKC function e.g. Prostaglandin
- Cis-UCA in the epidermis may be produced by conversion from trans-UCA via UVR. On exposure 60% UCA is converted and leads to dose dependent suppression of NKCs, possibly by down regulation of the secondary messenger system of NKCs (Gilmour 1993).UVR also reduces psoriatic plaques by inhibition of ornathine decarboxilase activity and is known to lead to elevation of PKC activity in mice fibroblasts.

1.7 The History of Phototherapy

The original forms of phototherapy date back over 3000 years when the Greeks used the sun to treat certain skin conditions and topically applied plant extracts to improve pigmentation. In the 1700s rickets was common and it was found that the sun helped to prevent this condition, although the skins function in vitamin D production was not understood. Light was also used to treat skin and bone tuberculosis and today heliotherapy is still used in certain areas of the world eg. The Dead Sea where people travel hundreds of miles to receive its healing powers. The sun was the original source of UV radiation, having an MED of 20 minutes at midday in June at 41° latitude. The significance of this source of UVR is the fact that it is free, however, the variations in weather coupled with seasonal changes in solar UV intensities in Britain, it is an unrealistic therapy, so other alternatives are provided by the NHS. In other parts of the world heliotherapy is very important in the treatment of psoriasis. In Israel The International Psoriasis Centre has established a complex which consists of clinics, shops, hotels and restaurants so that sufferers may undergo a course of heliotherapy within a 'holiday'. The treatment involves sunbathing each day in accordance with a regime and daily bathing in the Dead Sea. Creams are applied frequently throughout the day under the guidance of trained nurses and dermatologists. The Dead Sea is 400m below sea level and the majority of erythemal-causing UVB rays are removed by increased passage through the atmosphere and because there is a high evaporation rate which leads to a very humid environment. These factors enable patients to bathe in

the sun for longer time periods than normal and thus, the centre is extremely beneficial in many cases. The Dead Sea contains 300g/l salt and patients return with increased skin tissue levels of magnesium, calcium and potassium and raised circulatory concentrations of bromine and selenium. But whether these compounds are also important in the treatment is unknown.

A major breakthrough in the therapeutic use of light came from Neils Finsen in 1890 through his treatment of tuberculosis with carbon arc lamps and his treatment of lupus vulgaris with the same equipment earned him the Nobel Prize in 1903 (Diffey 1982). Following Finsen's work came the work of Alderson in 1923, proposing the beneficial use of the newly invented mercury vapour lamp.

The first recorded form of crude PUVA in the western world came from Axmann in 1918 who used oil of bergamot on unpigmented areas of skin and vitiligo was treated similarly but with psoralen in 1948 by El Mofty. The breakthrough in systemic psoralen and UVA treatment came from the work of Parrish et al in 1974. They published information that demonstrated the use of PUVA for psoriasis and a new form of treatment became available which is particularly important for treating premalignant and malignant conditions such as mycosis fungiodes, Nekams Disease and lymphomatoid papulosis, as well as psoriasis, eczema and light sensitivity conditions.

UVB phototherapy was originally used in conjunction with other topical treatments e.g. tar, sulphanilamide and dithranol and at the beginning of the 20th century UVB was not thought to be beneficial if administered alone (Ellis et al 1948). Epstein analysed UVB therapy in 1947 and concluded that UVB is completely ineffective in the treatment of psoriasis if the skin is not firstly sensitised. He found that administration of UVB 1-3 times/week accompanied with sulphanilamide and tar to be very beneficial. Ellis (1948) also found that UVB alone was ineffective but the paper he provided was not detailed enough. He did not describe regimes used or doses and the patients were only treated for 2 weeks at a time. It was also unclear if erythemal doses were administered. In 1925 Goekerman observed that coal tar topical treatment plus UVB therapy

produced increased beneficial effects to light therapy alone and he concluded that tar is a photosensitizer (Young 1972).

Another regime was described by Ingram in 1953. The protocol is similar to Goekermans except it involves coal tar paste, zinc oxide and paraffin, tar baths instead of soap and water or the use of undiluted picas carbonis instead of crude coal tar, all of which seem to produce better results. Treatment is repeated every 24 hours. The dithranol is an oxidising agent and burns the lesions and the stockinet acts as a compress to intensify treatment (Ingram 1953).

In 1970 Young et al performed experiments which indicated UVR tends not to be an essential part of dithranol treatment using Ingrams regime and significant success can be achieved without UVR.

In 1977 Parrish et al provided outstanding evidence that UVR can be successfully administered alone, if given to erythema. In 1976 Fischer performed experiments using different wavelengths of UV (313, 334, 365 & 405 nm). The results indicated that treatment of psoriasis 5 times/week was most effective when erythema was produced at 313nm wavelength. Once it was universally accepted that different wavelengths of UV have different effects on the skin, studies involving manipulation of the spectrum were undertaken and in 1981 Parrish and Jaenicke performed an exceptional study using monochromatic wavelengths of UV in psoriatic patients. The effect of wavelengths 254, 280, 290, 296, 300, 304 and 313nm were determined and the course was 24 treatments over 4 weeks. Results were examined and it was found that UVC has no therapeutic effect and easily produces erythema. Treatment with 296nm was found to have varying effects and in some cases no significant effect and in others, complete clearance. 300 and 304nm treatments produced clearance at doses equal to or just greater than the MED and 313nm completely resolved the psoriasis in all 4 patients. The authors concluded that UVC is phototoxic, UVB is very effective and can be used at levels less than MED, and UVA is ineffective at acceptable exposure times. Having identified the optimum wavelength for treatment, projects were initiated to produce a

more effective lamp and the narrowband UVB lamp was manufactured in 1984-5 (Anderson et al 1984).

1.8 The Practice of Photochemotherapy (PUVA)

Since it was established that phototherapy alone is beneficial a variety of regimes have been developed for UVB and PUVA. Although a relatively large dose of UV is given in the treatment of psoriasis it would be ineffective and dangerous to administer the dose in 1 treatment. Therefore the treatments are fractionated and cumulative doses are administered. Through fractionation the skin is allowed to adapt in order to allow greater increments to be given and the ultraviolet radiation has a progressive effect on the immune system, the keratinocytes and the inflammatory cells of the patient.

1.8.1 PUVA Therapy

PUVA is a combination of UVA radiation and the administration of photoactive chemicals - psoralen. Psoralens are a group of furocoumarin compounds that are isolated from particular species of plants e.g. lime, lemon, parsley, parsnip and celery. Once digested the psoralen reversibly binds to cytoplasmic membrane proteins throughout the body. Circulatory psoralen is degraded in the liver and excreted as an undetectable biproduct. The most frequently used oral psoralen is 8-methoxypsoralen isolated from *Amni Majus* and was originally used as a topical agent to treat leucoderma (El Mofty 1948). PUVA can be administrated in 3 basic ways: tablet treatment, topical treatment or bath treatment and it is used to treat conditions including psoriasis, vitiligo, eczema, lichen planus, graft versus host disease, pityriasis lichenoides chronica, cutaneous T cell lymphoma (mycosis fungoides), urticaria pigmentosa and photosensitive disorders. In the treatment of psoriasis lesions usually clear within 6-8 weeks.

Systemic Treatment

8 methoxypsoralen (8 MOP) is the usual oral drug administered although 5- and 3-methoxypsoralen are also available and they normally have less severe

side effects than the 8-MOP alternative. Each 8-MOP tablet contains 10mg psoralen and the dose taken depends upon the patients weight. The usual dosage is 0.6mg/kg.

The tablets are taken 2 hours prior to UVA administration because the maximum plasma concentration of 8-MOP occurs at approximately this time after ingestion. The side effects of psoralen include nausea, depression, insomnia, nervousness and dizziness.

Psoralen Bath Lotion

Some hospitals, including Dryburn Hospital, do not have bath PUVA facilities available. Bath psoralen is 1-1.2% solution in an aqueous base and the patients are required to soak in the bath of solution at 2.6mg/l for 15 minutes. UV opaque spectacles are not necessary and the adverse effects of oral psoralen are not usually seen, however, potential burning risks are present if the psoralen is not carefully mixed in the bath water.

Psoralen topical lotion/gel/paint

PUVA lotion is 0.15% in aqueous solution, the paint is 1-0.15% in solvent solution and the gel is 0.005% in aqueous solution. The solutions are applied to affected areas as a thin film 15 minutes before irradiation and removed after treatment. No adverse effects are seen and application by a skilled nurse/physiotherapist rarely leads to burning through uneven distribution.

Courses normally consist of 10-30 treatments over a period of 4-12 weeks. The frequency of exposure and the length of course depends upon the condition and the severity and is normally prescribed by the doctor. In some clinics the first dose of UVA is administered depending upon the patients skin type and the usual starting dose is 0.5-1J/cm2. Prior to administration of PUVA therapy patients are given a full blood count and kidney and liver function tests. This is not necessary for UVB treatment as oral tablets are not taken. Histological examination of the skin may be carried out in certain cases. Some practices perform a minimal phototoxic dose (MPD) test. MPDs are performed in a similar way to the MED measurements I am under taking for this project. The

patients have the procedure thoroughly explained to them for maximum efficiency and the test is performed on disease free skin, normally on the back, arm or buttock. The skin is exposed to UVA at varying doses, either through apertures containing attenuators with different sized holes or by covering the skin with a cloth/plastic sheet that contains a grid of holes of differing sizes. The resulting MPD is then used to determine the starting dose. If no erythema is seen, the patient is questioned as to whether the psoralen was taken correctly and, if not, the test is repeated. If the test was performed adequately a 30% increased dose can be administered as the first dose. For topical application 70% MPD. is administered and the test is performed 15-30 minutes after application. The results are usually read 72 hours after the test is performed. PUVA is normally administered 2 times per week and erythema reaches optimum after 72 hours. Clearance of psoriasis normally occurs after 30 treatments.

1.9 The Practice of Phototherapy

UVB is administered in a similar manner. Prior to treatment a MED test may be performed to establish a starting dose and 70% MED is safe to administer. The MED is established by the process similar to that described previously. For UVB therapy, erythema reaches a maximum 8-24 hours after exposure and therefore treatment may be given every day if necessary. However, administration normally occurs 2-3 times per week and clearance of psoriasis is seen after 20 treatments.

1.9.1 Action spectrum for healing of psoriasis by phototherapy

In 1981 Parrish et al determined the most effective wavelengths for the treatment of psoriasis using monochromatic radiation. They found wavelengths below 300nm to be very erythrogenic, 10 times more so than the 310-315nm range and the carcinogenic properties of UV radiation are also greater in these broadband lamps. (van Weelden et al 1984). Broad band lamps produce radiation in the region below 280nm and evidence indicates that UVC radiation

is ineffective in the treatment of psoriasis, producing burning rather than any therapeutic effect. (van Weelden et al 1980). Further studies suggest that the most effective wavelengths for treatment are 295-310nm and below 295nm the therapeutic effect is significantly reduced (Diffey and Farr 1996).

In 1984 van Weelden and van der Leun demonstrated that the effectiveness of phototherapy could be much improved by the use of a narrow band of UVB. If UVC is reduced, so are erythema. This led to the development of the TL01 lamps which produce emissions peaking at 311nm (± 2nm) and a smaller peak at 305nm. In 1986 van Weelden and van der Leun compared the efficiency of narrow band lamps to wide band lamps by treating one side of the body with broad band UVB and the other side with narrow band UVB. The patients were irradiated until erythema was produced. The results indicated that the narrow band lamps were significantly more effective in psoriatic treatment. ($P=<0.05$).

1.9.2 TL01 Phototherapy

The TL01 lamps use has steadily increased over the last 30 years. The dose of UVB that can be given during any one treatment is limited by the level of erythema that exposure produces. Philips TL01 lamps emit a narrow band of UV radiation peaking at 311-312 nm. The lamp manufacturers altered the phosphors in the lamp rather than the filter glass itself in order to alter the energy distribution of the lamp. The success of the lamp is due to its ability to exclude shorter wavelengths of UV which are erythrogenic but do not benefit psoriasis. Lower exposure doses are required as the lamp is more intense and there is a potential for reduced cumulative doses if a successful regimen is produced but higher cumulations of radiation can occur because of the reduced erythrogenic effect of the lamp (Parrish 1981).

Initially, regimens for the TL01 were incorporated from broadband protocols. Many studies have subsequently been undertaken over the past 20 years, involving analysis of regimens. The intent is to produce a suitable protocol with minimal cumulative doses, minimal painful erythema occurrences and minimal treatment sessions with maximum results (Van Weelden 1990).

There are 2 basic regimens for the use of TL01 phototherapy as outlined below.

The most commonly used regimen involves a treatment programme where there is a starting dose of 0.3J/cm^2 and subsequent stepwise increases e.g. 0.3, 0.5, 0.9 J/cm^2. The subsequent treatment dose depends upon the previous dose and the skin's erythemal reaction to it (no erythema, definite erythema or equivocal erythema). Patients move through the treatment chart until an erythemal response presents. The patient then moves down the chart receiving appropriate treatment doses. The treatment process is dependent upon patient feedback (see appendix 1 for treatment chart).

The second treatment regimen involves MED (minimal erythema dose) testing the patient prior to treatment initiation. The MED is determined using a TL01 lamp mounted into a phototesting apparatus. The MED is determined 72 hours post test and initial doses are administered at 70% MED. The increments for further treatments are 40%, 20% and 10% depending upon the extent erythema produced by previous treatment sessions and due to the patients skin type which is confirmed by taking a patients history and through objective determination of the skins melanin levels. Treatment continues until the patient's psoriasis is cleared to a suitable level (Collins 1995).

Regardless of the method of administering phototherapy, during the treatment programme trained staff are required to assess the patient's progress in-between treatment sessions. Skin typing, patient history, physical examination and verbal enquiries are all used to determine UVB radiation treatment levels during the treatment course (Gordon 1998). In 1994 Dootson performed a study that indicated that only 28% Phototherapy centres in the UK use this method of treatment. The initial UVB dose should be sufficient to ensure that the radiation has a therapeutic effect without causing excessive erythema.

It was Fischer in 1976 that suggested that this level is typically 70% of the MED. A study performed by Gordon et al in 1998 also demonstrated that skin typing alone can not be a successful way of determining a radiation programme or initial radiation doses.

Many studies have been carried out in order to determine the therapeutic differences between TL01 Phototherapy and TL12 and also comparing TL01 to PUVA. (A comprehensive table of comparative studies can be seen below.)

Studies comparing TL01 to TL12 (e.g. Karvonen et al 1989; Green et al 1988; Picot et al 1992) have demonstrated that the TL01 lamp is superior in efficiency to the broad band TL12 lamp. In 1986 and 1988 van Weelden et al performed studies that demonstrated how successful the TL01 lamp is. In 1988 the study involved 10 subjects. 1 side of the patient was treated with broad band UVB and the other with narrow band. The patients were hospitalised and exposed to radiation from both lamps simultaneously. One lamp was situated at the back of the cabinet and 1 at the front. Therapy was performed 3 times/week for 10 treatments in 8 patients and 2 times/week in 2 patients. The effects measured were based upon the amount of erythema produced, scaling decreases and severity of the condition after treatment. It was found that TL01 treatment was the more effective treatment of the two in 9 out of 10 patients ($p<0.05$). During this study they also compared the tumour promoting potential of the lamps through exposing mice to the lamps until erythema and oedema occurred. All animals developed tumours but those receiving TL12 treatment developed the growths at significantly earlier stages in the treatment. ($P<0.01$). More recent studies contradict this information. Flindt Hanson (1991) performed irradiation studies on hairless mice 5 days/week for 30 weeks using TL01 and TL12 phototherapy. It was found that tumours appeared significantly earlier in TL01 treated mice. Wulf (1994) and Gibbs (1995) also confirmed these results and it is now thought that TL01 phototherapy is in fact more carcinogenic than alternative broad band TL12 treatment. This is because UVA is thought to play an important role in skin protection, possibly through enhancing the repair of

pyramidine dimers and reducing free radical formation. However, because the TL01 lamp produces results quicker and maintains remission for longer periods of time, these lamps still remain more popular in the majority of hospital phototherapy departments. A similar study was performed in 1996 by Gonzalez et al who determined the tolerance of human skin to UVB. The study involved 90 patients with plaque psoriasis and MPEs were determined 24 hours after exposure to broad band UV. The test involved exposure to 15 apertures 1.3 cm in diameter. The sites decreased in doses from 150-10 mJ/cm^2 with increments of 10 mJ/cm^2 each. Phototests were performed every 2-3 weeks and the patients were treated 4 times/week. The results indicate that the minimal perceivable erythema (MPE) increases rapidly in the first two weeks for all skin types and plateaux by the sixth week. The authors found that the MPE of those with an initial MPE of 20-50 mJ/ cm^2 began to decrease again after the sixth week whereas those with an initial MPE of 60-100 mJ/cm^2 remained constant until the eighth week. From the results a 'tolerance factor' (TF) was expressed as:

$$TF = TF_{max} \ [1 - e^{-t/\tau}]$$

where TF_{max} is the maximum value the tolerance factor might attain; t is the number of weeks of treatment; and τ is a characteristic time over which the skin develops 63% of TF_{max}.

The group concluded that tolerance is due to hyperpigmentation, thickening of stratum corneum and probably a number of other complex factors that lead to a decrease in tolerance after multiple exposures.

TL01 – PUVA studies have generally found the therapeutic effects of PUVA and narrow band UVB to be similar and UVB is more favourable due to the reduced post-radiation effects; clearance rates and cumulative dose levels were found to be insignificant but because psoralen consumption is not

required with UVB treatment, TL01 treatment is more favourable: eye protection is not required post-treatment, the patient does not feel dizziness or nauseous, there is a reduced drug cost implication and TL01 phototherapy is suitable for both pregnant ladies and children (Takew 1996). In 1990 van Weelden compared PUVA to narrow band phototherapy and found PUVA to be superior in treating in clearing lesions from the extremities whereas TL01 therapy is more effective at clearing lesions from the trunk.

In 1998 several studies compared regimens where low and high dose increments were administered. Clearance times, cumulative doses, severe erythema episodes and the number of treatments per week were all investigated and compared. The study of Hofer et al in 1998 involved 13 patients who were treated 3-5 times per week. 11 patients completed the trial and the patients randomly received a low dose regime to one side of the body at 35% MED and the other side of the body received 70% MED. The results indicate that initially the response was better from the high dose treatment but as treatments continue a satisfactory response is seen through both treatment regimens. After 3 weeks of treatment the clearance level is actually equal from both treatment protocols and only 4 more treatments were required from the low dose regimen (16 rather than 12 treatments). The lower dose regimen acquired a significantly lower cumulative dose of radiation (9.4 J/cm2 as compared to 14.0 J/cm2 using the high dose regimen.) Therefore a lower dose regimen is much more advantageous. Wainwright performed another study involving the comparison of high and low dose increments in 1998. This half body study involved 20 patients being treated 3 per week. Half the body received 70% MED for the initial treatment and then 40%, 20%, 20% or 0% increases depending upon the erythemal response. The other half of the body received the low dose regimen, which involved delivery of 70% MED, followed by 20, 10 or 0 % MED radiation dose increments. Again, subsequent dose levels depended upon post treatment erythema. The results of this study collaborate the results of Young's investigation; both regimens produced similar clearance levels, a greater number of treatments were required for the lower

dose regimen but a lower overall cumulative dose is achieved. The lower dose regimen also produced less potential for painful erythema (twice less likely) making this regimen more favourable. There were no significant differences between remission lengths for either regimen.

Studies have also been carried out in order to determine the minimal number of treatment sessions required per week in order to provide effective treatment. In 1998 Dawe et al studied 9 patients receiving treatment 3 and 5 times per week. Half body suits were worn and treatment was administered until clearance was achieved. It was hypothesised that the 5 treatments per week regimen would be the most effective stimulating clearance with fewer UVB exposures and a lower cumulative dose than the 5 times per week regimen. The study indicated that 5 treatments per week clears psoriasis quicker (35 days rather than 40) but at the expense of a higher cumulative dose and more treatment sessions (median 23.5 treatments for the 5 treatments per week and 17 sessions for the 3 treatments per week). Painful erythema was also more likely with the higher weekly treatment regimen and there was no significance in the relapse time. Therefore, in order to reduce cumulative doses and treatment session numbers, 3 treatment sessions per week is more suitable. Studies continue to be performed in order to determine a safer and more therapeutic protocol and this study also aims to provide a deeper insight into narrow band UVB phototherapy.

NAME	*YEAR*	*JOURNAL*	*STUDY DETAILS*
Van Weelden	1988	Br J Dermatol 119: 11-19	UVB progress
Green	1988	Br J Dermatol 119:691-6	NBUVB progress
Karvonen	1989	Acta Derm venereol 69:357-9	NBUVB progress
Larko	1989	Acta Derm venereol 69:357-9	NBUVB progress
Van Weelden	1990	Acta Derma Venereol 70: 212-15	NBUVB v PUVA
Storbeck	1991	Z Hautkr 66: 708-12	NBUVB v BBUVB
Green	1992	Phys Med Biol 37(1) :1-20	TL01 v PUVA
Picot	1992	*Br J Derm* 27:509-12	TL01 v TL12
Bisland	1993	Br J Derm 129; (6) 708-12	TL01 v PUVA
Gibbs	1993	Photochem Photobiol 58; 643-7	NBUVB v BBUVB
Moseley	1993	Br J Derm 128 96-; 704-6	UVB erythema
Ortel	1993	J Am Acad Dermatol 29; 736-40	UVB v bath PUVA
Storbeck	1993	J Am Acad Derm 28; 227-31	NBUVB v BBUVB
Wulf	1994	Photoderm Photoimmunol Photomed 10;192-7	Carcinogenesis of NBUVB v BBUVB
Collins	1995	Br J Derm 133; 653-67	TL01 Rx regimen for children
Collins	1995	Br J Derm 132;956-63	TL01 Rx Regimen
Gibbs	1995	J Invest Derm 104; 359-63	Tumer potential BBUVB v NBUVB
Anonymous	1996	Br J Derm 137; (3) 327-30	TL01 Appraisal
Tanew	1996	J Inv Derm 106; 84	NBUVB v PUVA
Dawe	1998	Br J Derm 138; (5) 833-9	TL01 Rx 3v4 times/week
Gordon	1998	Br J Derm 139; (5) 811-4	Phototesting prior to treatment
Hofer	1998	Br J Derm 138; (1) 96-100	High v low dose regimens
Wainwright	1998	Br J Derm 139; (3) 410-4	TL01 regimens
Der-Petrossian	2000	Br J Derm 142; (1) 39-43	PUVA v NBUVB

BBUVB = broad band ultraviolet radiation B NBUVB = broadband ultraviolet radiation Rx = treatment

1.10 Outline Of My Study.

Exposure doses are increased during the course to maintain an effective radiation dose at the epidermal basal layer as the skin adapts by hyperplasia and melanin pigmentation. The algorithm we use to increase exposure doses on subsequent treatments is based upon what is known about the adaptation of the skin following repeated exposures to broadband sources of ultraviolet radiation, as described above. However, we are using the TL01 narrow band fluorescent lamp and whilst this lamp has been designed specifically for the treatment of psoriasis, no established regimens for its use exist and it is likely that our present regimen is sub-optimal. The purpose of this study is to investigate how the erythemal response of the skin changes during a course of TL01 phototherapy in order to develop an effective regimen.

2 MATERIALS AND METHODS

2.1 Patient Population

Over the period of one year, 58 patients (aged between 18 and 72 years, mean 44 years; 28 female) referred to Dryburn Hospital Phototherapy Department for TL01 UVB treatment took part in the study. The majority of patients were being treated for psoriasis, however, 15 patients were diagnosed otherwise; 4 chronic superficial scaly dermatitis, 4 polymorphic light eruption, 4 lichenoides chronica, 1 pruritis, 1 eczema and 1 chronic superficial scaly dermatitis.

2.2 TL01 Phototherapy Unit

Patients were treated in a whole body unit incorporating 48 Philips TL01 lamps (Canterbury Instruments). The narrow band TL01 lamp is a relatively new addition to lamps available for phototherapy. It has an emission spectrum peaking at 311nm with a bandwidth of 2nm. The lamps were 2m in length mounted in 6 rectangular panels, the panels being arranged in a hexagon which constituted the treatment unit. Each panel incorporated 8 lamps 7.5cm apart. (see Fig 2.1). There were two doors to the unit incorporated into the front of the machine so that the UVB radiation was uniform around the patient and the patient was completely enclosed in the machine. Within the unit there was an emergency cord to enable the patient to stop treatment at any point if necessary. The doors were also able to open from the inside and this too stopped treatment if required. The exposure time for the patient was entered into the unit via a separate electronic timer located to the side of the machine and a mechanical backup timer was also set to prevent over exposure from occurring.

2.3 Whole Body Phototherapy TL01 Regime

UVB exposure produces erythema, which peaks 8-12 hours later and normally, fades within a few days. Therefore the sessions are normally given at least two days apart. The erythema produced from ultraviolet radiation limited the

exposure dose that could be given to the patient at any one time. Therefore, the treatment was fractionated and given, usually, over a period of 8 weeks. The duration of the treatment course depended upon variables such as the extent of the condition, the response of the skin and the attendance of the patient.

Exposure doses were increased during the course of the treatment in order to maintain an effective radiation dose at the epidermal basal layer as the skin adapted to the radiation by hyperplasia and melanin production.

The regimen used in Durham Phototherapy Department was based upon knowledge of skin adaptation upon exposure to broad band UVB since narrow band UVB, designed specifically for the treatment of psoriasis, is a relatively new concept with very little published evidence on the relationship between exposure and skin adaptation.

Patients admitted for a course of treatment were prescribed the course for (usually) 2 or 3 months. 38 patients were prescribed a course of 2 treatments/week and 18 patients were prescribed 3 times/week. 1 in-patient was treated 5 times/week and 1 in-patient was treated 7 times/week. 16 or 24 treatments were usually administered. A measure of photoadaptation, expressed in terms of the minimal erythema dose (MED), was determined between 1 and 13 times, with a mean of 5. Whole body exposure doses were increased logarithmically and recorded on the patients' record chart, which was designed for ease and accuracy, containing a predefined protocol for the patient based upon their response to the previous treatment. Initial treatment was given at 0.3 J/cm^2, increasing by 0.2 J/cm^2 until erythema was noted, normally this occurred at 0.5 or 0.7 J/cm^2 Once erythema had occurred doses were initially reduced and thereafter increased by fractional increments as treatment progressed. The initial increment was 30%, falling to 20%, 10% and 3% by the 5th, 10th and 20 th subsequent exposure, respectively. If moderate erythema occurred or if patients missed 2 or more treatments, empirical changes to the regime were applied (see appendix 1).

2.4 *Phototesting apparatus*

The phototests were performed using a single Philips TL 40W/01 lamp housed in a fully enclosed luminaire. Surrounding the lamp was a polycarbonate lamp diffuser, which was opaque to UVB radiation; therefore additional shielding was not required. Within the lamp diffuser there were 10 apertures, regularly spaced, each 8mm by 12mm. The apertures were designed to allow a range of doses to be administered simultaneously. One aperture remained open and the remainder were backed with metal foil, perforated with a grid of holes that were differing in size (Fig 2.2). The foil used allowed transmission of UV and did not vary with temperature, wavelength or the lifetime of the equipment. Each aperture increases the exposure dose by 26% giving a dose range of 8:1.The lamp was fitted with a digital electronic integrating dosimeter which terminated irradiation when the desired dose in the open aperture was reached. Irradiance from the lamp changed, depending upon factors such as temperature, lamp age and main supply voltage. The lamp was supported on a wall at an adjustable height to allow access to the outer aspect of the upper arm. It was situated in a small enclosed room in order to give the patient a sense of privacy and therefore encourage the patient to co-operate and produce the best results possible.

2.5 *Phototesting technique*

An initial phototest was performed prior to the patient's first treatment. The outer aspect of the patients upper arm was irradiated using the technique described previously. The irradiation site was then covered with a sheet of UV opaque card. The patients were given their whole body treatment and the card was then removed from the patients' arm. On the second visit to the department, 1 - 7 days later (mean 3 days), the just perceivable erythema on the upper arm was determined using visual assessment (Fig 2.3). Ideally, erythema threshold should have been determined 24hours post-test as it is known that UVB erythema is maximal 7-24 hours after exposure. This, however, was not possible due to the nature of the study where patients are involved. It is inevitable, therefore, that the accuracy of the results will be

decreased through the inability to acquire accurate readings at the most idealistic time period. However, because large numbers of patients were used in the study and because readings were always taken under the same environmental conditions all inaccuracies have been minimalised as for as physically possible. In order to achieve reproducibility, the assessment was always performed in the patients' cubicle, where the light was of constant illuminance. The patients were given their second whole body irradiation with no shielding over the phototested area to allow full treatment to occur. Phototests were repeated on several occasions during the subsequent treatments in order to determine the effect of narrow band UVB radiation upon skin adaptation.

In order to determine if the LOW range (1.5 J/cm^2 at the open aperture) or the HIGH range (3 J/cm^2 at the open aperture) should be administered the following strategy is employed:

- if the previous dose range was LOW and 3 or more dose sites showed erythema on the last visit the dose range was set to LOW
- if the previous dose range was LOW and only 1 or 2 sites showed erythema on the previous test, the range was set to HIGH.
- if the previous dose range was HIGH the dose range was kept at HIGH

The initial phototest was always set at LOW but exceptions were made if the patient was not Caucasian or if extremely tanned, where the phototest started on HIGH. Personal observation has shown that patients with psoriasis do tend to have a greater tan than the average British person which is probably due to the positive effect that UV radiation has upon the condition. Therefore tanned patients were included in the study. However, if patients were particularly tanned (beyond what we would subjectively consider to be the 'normal' range). They were excluded from the study. Inclusion of such subjects would alter the results and lead to false conclusions.

For each phototest care was taken to ensure that the test was not performed on skin which had already been used for the test and the right and left arm

were used alternately. This was done through recording phototest positions on a chart (see appendix 2).

All information was documented both in a written record sheet and on computer using a spreadsheet prepared by myself using Microsoft Excel. The patients' record sheet provided the following details:

name
age
sex
frequency of treatment
any nonattendances or cancellations.

And for each phototest:

days since last treatment
number of treatments already attended
the range setting on phototesting apparatus
the arm used
days MED read following the test
MED (number of sites where erythema was present).
MED (J/cm^2)

Each phototest was also recorded on computer so that collective data analysis could be performed and the information was readily available for statistical analysis. The data was analysed using MED ratios, which are expected to increase as skin adaptation occurs.

$$\text{MED ratio} = MED_n / MED_0$$

MED_0= baseline minimal erythema dose measurement.

MED_n = minimal erythemal dose after n number of treatments.

The MED ratio determines the extent of photoadaptation which has occurred since the initiation of the treatment course. It is a measurement of the increase in adaptation to UVB radiation due to the treatment administration.

The aim of the project was to develop a skin adaptation model. It is known that UVB leads to hyperplasia and decreases in UVB levels lead to skin thinning. During UVB therapy, skin is actively thickening after UVB exposure and thinning between treatments, particularly if there are several days between exposures. Analysis of the data was aimed at providing a mathematical model that will enable optimum doses of UVB to be administered throughout the course particularly if treatments are missed or delayed (see appendix 2 for record sheet).

Fig 2.1 The TL01 whole body phototherapy unit used for treatment

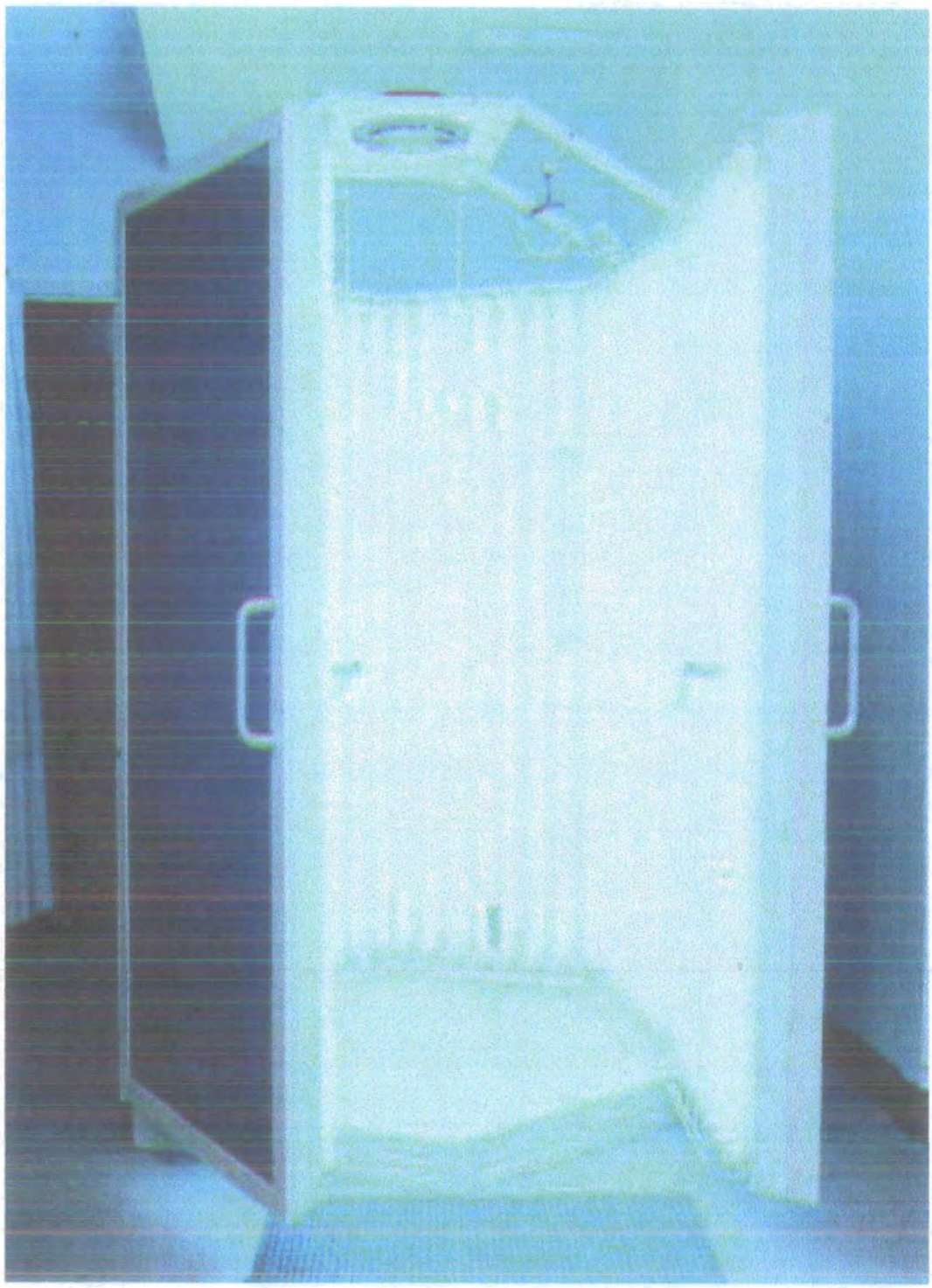


Fig 2.2 The phototesting apparatus containing metal foil attenuators that allowed simultaneous delivery of 10 different doses of UVB

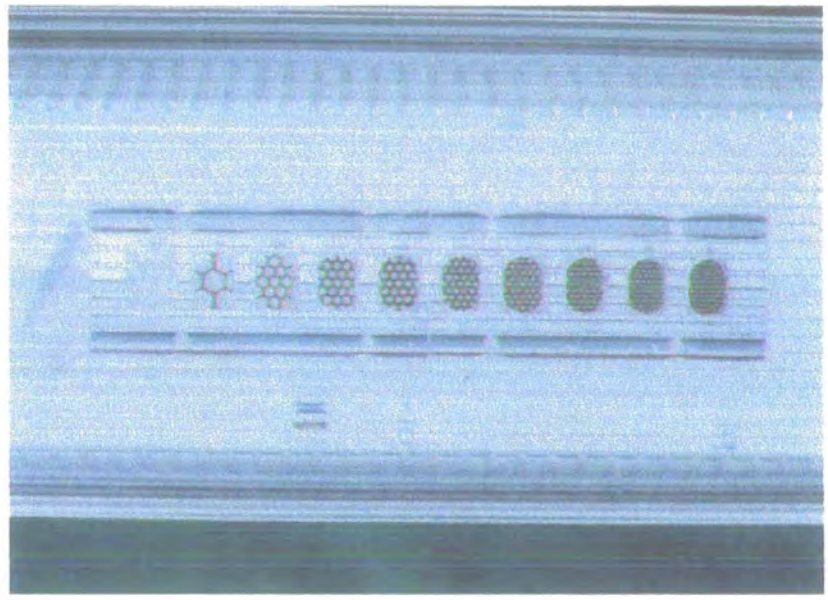
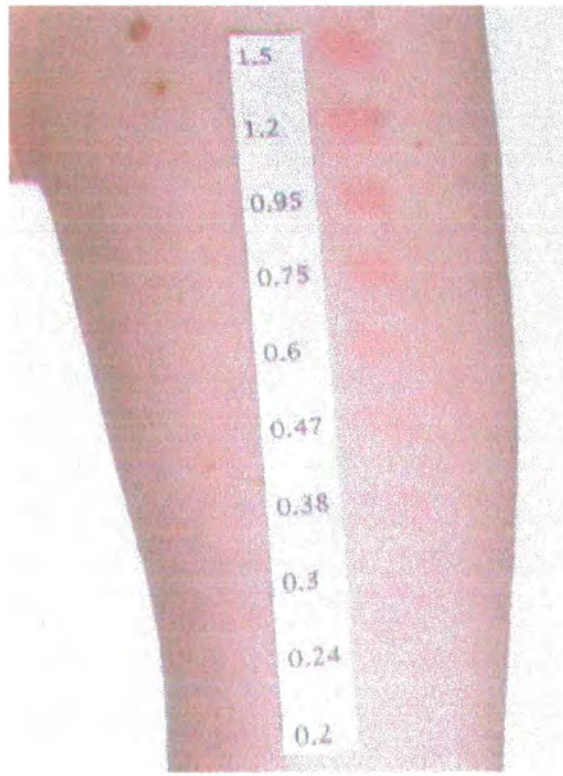


Fig 2.3 An example of the graded erythematous reaction 24h after phototesting. The MED in this patient was assessed as 0.47J/cm^2



3 RESULTS

3.1 Descriptive Statistics

A total of 58 patients were enrolled and 330 MED measurements were made, 272 of which were during treatment (MED_n) and 58 baseline measurements were made.(MED_0). The term MED_n indicates the MED after *n* treatment sessions. For each patient tested, the diagnosis was recorded (Table 3.1) along with the duration of treatment, number of treatment sessions and cumulative doses.

TABLE 3.1 Summary of Phototherapy Course (values are medians)

Diagnosis	Number of patients	Duration (weeks)	Number of sessions	Cumulative dose(J/cm^2)
Psoriasis	43	8	16	16
CSSD	5	7	16	17
PLC	5	6	12	11
PLE	4	7	16	9
Eczema	1	4	9	3

Prior to treatment the baseline measurements (MED_0) were made and continuous assessment of the tolerance was made by repeating MED measurements (MED_n) following *n* treatment sessions. A summary of the phototests performed is shown in Table 3.2.

TABLE 3.2 Summary of Phototests

No. phototests during treatment course	No. Patients
≤3	12
4-6	29
7-9	14
10-12	3
TOTAL	58

When the skin is exposed to UV radiation photoadaptation occurs, this involves epidermal hyperplasia and pigmentation. If the skin is not exposed to UV radiation the epidermis thins and depigmentation occurs. Tolerance is a measure of the relationship between these two processes.

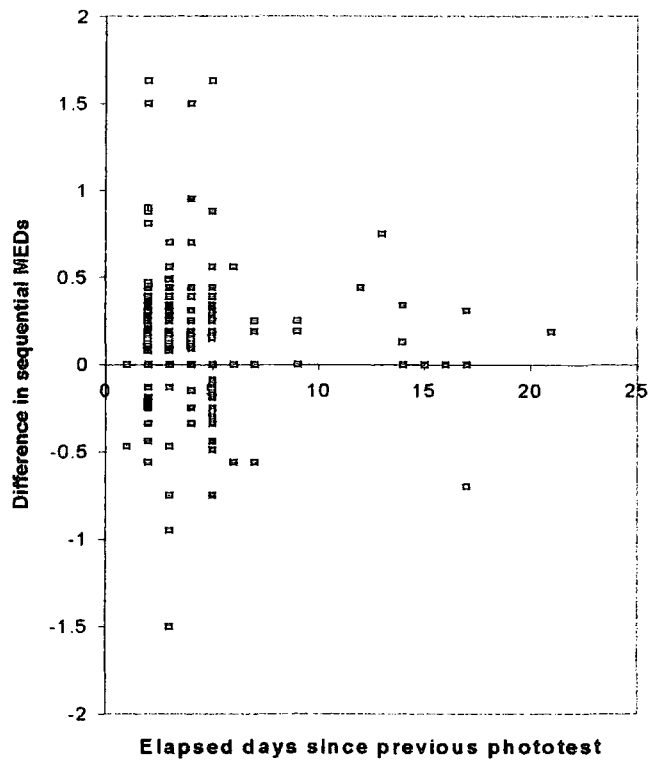
Tolerance of the skin can be described in the following model:

$$\text{tolerance} = (\text{photoadaptation})(\text{recovery})$$

and can be expressed as:

$$T_n = [MED_n] / [MED_0]$$

It is expected that the recovery time becomes more significant as the time between exposure increases. In order to examine this, the difference in tolerance between successive MEDs was determined (ΔMED) and the number of days that have elapsed since the previous phototherapy exposure was plotted below. Association analysis showed no relationship between these 2



variables (Spearmans coefficient of rank correlation, P = 0.3).

The data can be divided into 2 groups

- ΔMED values where the previous exposure was 5 days or less

- ΔMED values derived when more than 5 days have elapsed, due to the patient missing one or more treatment sessions. A Mann-Whitney test showed no significant differences in median values for the 2 ΔMED groups.

3.2 Derivative of a Mathematical Model for Adaptation.

There was no significant relationship between the relationship between the elapsed days since the previous phototest and the ΔMED for those whose last treatment was <5 days and those whose treatment was >5 days. Therefore tolerance can be modelled using the following equation:

$$T_n = 1 + A\,[\,1 - \exp(-\lambda n)\,]$$

where λ is a parameter representing the rate of adaptation.

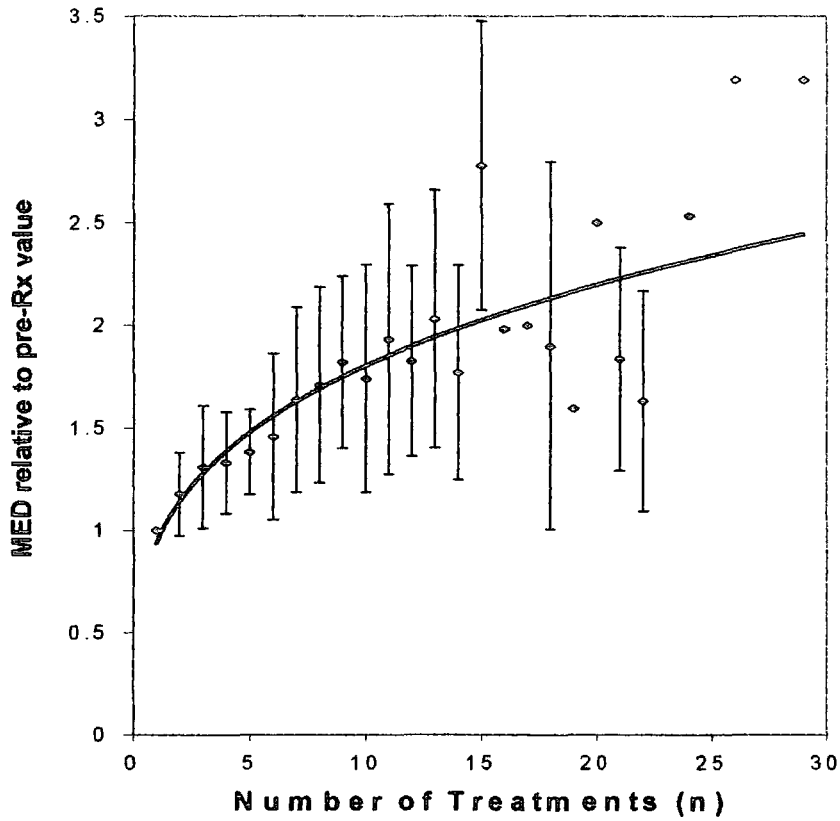
Iterative regression analysis was applied to the pooled set of patient data to determine the coefficients A and λ. In this technique, the coefficient *A* is 'guessed' so that the above equation can be transformed into a linear form:

$$\log\,[\,1 - (T_n - 1) / A\,] = \lambda n$$

The coefficient λ is obtained by linear regression and a 'goodness of fit' statistic calculated. The process is repeated by choosing the value of *A* which gives a minimum in this statistic.

3.2.1 Fitting the Model to The Experimental Data

The mean values (± 1 sd) of T_n at each treatment session were calculated and plotted in the following Figure.



From the regression analysis, λ and A were calculated, giving an expression for tolerance as:

$$T_n = 1 + 3\,[1 - \exp(-0.03n)]$$

From the expression it can be shown that the maximum mean tolerance is 4 (1+3). This value is less than that determined from studies derived from

broadband UVB lamps. In such studies the range has been 4.7 - 9.5, depending on the skin type of the subject. T_n was then used to revise the protocol for UVB narrowband phototherapy administration.

4 CLINICAL TRIAL

The data obtained in this study indicate that the differences in adaptation between broadband and narrowband UVB are only slight and therefore treatment protocols intended for broadband UVB treatment can be used during treatment with narrow band lamps. Narrow band lamps, however, appear to be more intensive in their therapeutic effects and lead to increased potential for excessive erythema, discomfort and inflammation. The study also enables a protocol of treatment to be produced that will enable administration of radiation at a higher efficiency with a smaller cumulative dose. The length of exposure is reduced per treatment and therefore the overall cumulative dose is also reduced.

4.1 Clinical trial

In order to determine the extent of improvement the 'new' protocol produced a clinical trial was developed which involved random allocation of patients to either the new protocol (*yellow* group) or to the pre-exisitng regimen (*green* group).

The clinical trial was carried out to compare a low dose regimen, based upon data derived from this study, to the usual protocol used in Dryburn Dermatology Department.

A similar type of study was performed in 1998 by Hofer et al, comparing the therapeutic effects of 'near and far' narrow band UVB phototherapy. Patients were treated 3-5 times/week and 1 half of the body was exposed to 70% of the MED (near exposure) and the other half was exposed to 35% of the MED (far exposure). Doses were increased by 40%, 20% or not at all depending if erythema was not present, only slightly present or very obvious, respectively. A severity index was recorded for each patient once a week, based upon desquamation, infiltration and percentage coverage. 11 patients completed the study and analysis of the courses indicated that both regimens were successful

in clearing psoriasis. The far regimen required 4 more treatments than the near regimen and the far regimen still produced similar responses but with less cumulative doses of UVB. Hofer et al concluded that overall the far regimen was most appropriate in treating psoriasis and other skin conditions.

In this clinical trial 48 patients were employed and randomly given either treatment regimen. 23 patients received the revised protocol (yellow group) and 25 patients received the usual treatment course (green group). The information was collected over a period of 6 months and the initial minimal erythemal dose was recorded (usual range 0.5-0.9 J/cm^2. Any excessive erythema that was encountered was noted and cumulative doses were calculated.

Prior to initiation of treatment each patient underwent a preassessment using clinical scores to determine the severity of the condition. The recorded scores were based upon the extent of psoriasis on the arms, trunk and legs. (1=severe 2= moderate 3 = mild) Scores were then totalled so that 3 was most severe and 9 was most mild. Post treatment scores were also collected by the nurse. The post treatment scores were based upon the % clearance that occurs in each area.

During the study the following data were recorded:

- Number of treatments per week
- Top row dose
- Cumulative dose
- Total number of treatments
- Pre-treatment severity score
- Post treatment severity score
- The number of excessive erythemas

In both regimens exposure was increased logarithmically until erythema was seen 48-72 hours later, i.e. on the patient's next visit. The radiation dose was then reduced and increased at a more gradual rate to accommodate the patient's skin tolerance rate.

The protocol for the green group had initial treatments of 0.3, 0.5, 0.7 and 0.9 J/cm^2. The patient moved across the chart until erythema was experienced, the next dose was taken as 80% of this dose and the further treatment doses were increased logarithmically. The yellow chart produced exposure doses that were similar but exposure increments were increased at a much slower rate. This resulted in a lower risk of erythema, discomfort and burning. If the trial was successful it could provide evidence that the protocol is effective. It will provide a protocol with a higher efficiency and a smaller cumulative dose. The treatment times will be reduced per treatment session and there will be less possibility of excessive, painful erythema, and potential carcinogenicity.

All other variables were maintained during the trial in order to enable accurate comparisons to be made. In both regimens exposure doses allowed continual radiation at the epidermal basal layer and upon discharge, the severity of the patients' condition was established and related to the pre-treatment score. The following scoring system was used:

- -1 worse
- 0 no change
- +1 moderate improvement
- +2 good improvement
- +3 very good improvement

Both regimes were prescribed for either 2 or 3 months and patients could have been discharged earlier if the condition had significantly improved. Discharge depended upon the opinion of the nursing staff at the time of the appointment and is confirmed by the doctor in charge. This prevented the patient from being exposed to more radiation than was necessary and therefore kept the cumulative dose to a minimum.

4.2 Results

The regimen used for each patient was selected randomly and the study involved both male and female patients. The conditions of the patients were

psoriatic only and severity ranged from 3-9 (average 6). On completing the treatment a second clinical score was collected. The post treatment was an indication of improvement and the range obtained was from 3-9 (average 6). Possible scores are 3 worse, 0 no change, 3 moderate, 6 good and 9 very good. Ideally, to eliminate bias, staff members should have been unaware which treatment regimen the patient was undertaking but this was unavoidable.

4.2.1 The Green Group

The green group of patients received the original phototherapy regimen and were treated for 6.5-13 weeks (median 8 weeks). After completion of the treatment course the severity score raised from 6 (range 3-9) to 7 (range 0-9). The average top row dose which produced the initial erythema was 0.7 J/cm^2 (range 0.3-0.9) and the patients were subjected to 13-24 treatments (median 16 treatments). The median cumulative dose was 16.9J/cm^2 varying from 6.7-49.6 J/cm^2 (Table 4.3).

Table 4.3 Summary of clinical trial data

Variable	Green median (range)	Yellow median (range)	P-value
Weeks of treatment	8 (6.5-13)	8 (3.5-12)	not significant
Top row dose (J/cm^2)	0.7 (0.3-0.9)	0.7 (0.3-0.9)	not significant
Total dose (J/cm^2)	16.9 (6.7-49.6)	12.7 (2.1-21.5)	0.008
No. treatments	16 (13-24)	16 (8-23)	not significant
Pre-treatment score	6 (3-9)	6 (3-9)	not significant
Post-treatment score	7 (0-9)	6 (3-9)	0.02

4.2.2 The Yellow Group

The yellow trial patients underwent treatment with a protocol devised from the results of this study. The median number of weeks of treatment given to

patients in this group was 8 (range 3.5-12), consisting of 16 treatments (range 8-23). The pre-treatment and post-treatment score was 6 (range 3-9) and the top row dose was 0.7J/cm^2, ranging from 0.3-0.9J/cm^2. The median cumulative dose was 12.7J/cm^2 (range 2.1-21.5J/cm^2) and during the course 22 patients experienced no erythema and only one patient was subjected to burning (Table 4.4).

Table 4.4 Incidence of burning

No. Burns	Green group	Yellow group
None	18	22
≥1	7	1
P-value (Fisher exact test)	*0.05*	

4.3 CONCLUSION

The two groups of patients were well matched in terms of total pre-treatment scores and both groups consisted of a comparable number of patients. Therefore the results of the green and yellow trials can be compared and the following conclusions can be drawn:

- There was no significant difference between the number of weeks of treatment administration for both groups.
- There was no significant difference between the top row dose for both groups.
- There was no significant difference between the number of administered sessions per week for both groups.
- Patients in the yellow group received a lower cumulative radiation dose than the green group (P=0.008).
- Patients in the yellow group experienced significantly less episodes of burning than the green group. 4 patients in the green trial experienced

one burn and 3 patients experienced two burns. In the yellow group only one patient was reported to have experienced one burn.

- The improvements of the patients' conditions were greater for subjects in the green group than in the yellow group as measured by the post-treatment scores.

5 DISCUSSION

5.1 Reliability of MED determination

The MED determinations were carried under the same environmental conditions, including ambient illumination, throughout the study in order to minimise random uncertainties and increase the accuracy of the study. Each MED was recorded by determining the number of sites that produced erythema. As far as possible I ensured that I was available for MED determination to minimise inter-observer bias. However, occasionally I was not present to assess the MED which was left to a member of nursing staff who had been previously shown how to assess MEDs.

Other difficulties arose from the differences in skin types. Patients of varying skin types pigment to different degrees and some patients presented erythema that had already reached a maximum and was deteriorating, whereas in other patients the erythema was still maximal. During the MED recordings I assumed that this would cause problems to the study and skin types would have to be considered to produce viable results. However, analysis of the data (see chapter 3) clearly indicated that skin type did not significantly effect the results and did not need to be considered when presenting a protocol for treatment. Personal tolerance variations are considered through the way in which individual patients move through the treatment chart and this has proved to be sufficient. I also thought that the time period between performing the test and reading the results may affect the data because erythema deteriorates with time but upon analysis this did not prove to be significant and it was not necessary to include them in the model for skin adaptation.

5.2 Fitting The Data To The Model

The aim of the study was to determine an effective regime for the treatment of skin conditions such as psoriasis using narrow band UVB phototherapy. The rate of adaptation and the maximum tolerance was found to be significantly lower than expected through studies involving broad band UVB and the mean

maximum tolerance was found to be 2.6, reached after 40 treatments at the current administration protocol. Previous studies using broadband UVB lamps found the tolerance level to be 4.7 - 9.5. The protocol used in the department is based upon these values and as a result it is often found that painful erythema results during the course of treatment. This can be explained using the results of the experiment because they indicate that the protocol chart increases the rate of UVB administration too rapidly and at a significantly higher rate than the rate of skin adaptation, therefore, too much radiation is being administered causing the erythema which is commonly seen.

Cumulative doses of radiation vary from 0.1 - 87.9 Jcm^{-2}. This value depends upon the number of treatments and the level of radiation administered during each treatment that is directly related to the tolerance level of the patient. Patients move across the chart from left to right during the treatment course until they experience the initial erythema then the patient proceeds down the chart moving towards the left (lower doses) only if necessary. The data collected during the course shows a wide variability of results, however, a pattern has emerged that indicates the level at which the 'average' individual adapts to narrow band UVB radiation. The variability of results will depend upon skin type, duration of treatment, number of treatment sessions, the period of time over which treatment occurs, the cumulative doses of the treatment, errors and the condition that is being treated.

5.3 Variations With Skin Type

The skin type of individuals is determined by establishing the amount of radiation that is required to produce erythema prior to the initial treatment. The protocol followed (see appendix 2) meant that the patients received increasing increments of radiation until the skin began to become erythemal. Erythema was usually found to be on the chest, stomach, back or thighs. At this point the course for that particular patient was changed, to follow a more gradual regimen in order to prevent overexposure leading to severe erythema

Skin Type	Property
1	always burns, never tans
2	sometimes burns, sometimes tans
3	rarely burns, usually tans
4	always tans, never burns

The majority of patients attending for UVB treatment were of the skin types 2 and 3, which means they could withstand some quantity of radiation before becoming burnt. A large number of patients were being treated for polymorphic light eruption and 4 participated in the study. For these patients the radiation had to remain low but it was important to include these patients in order to provide a protocol that could provide a regimen to suit everybody's needs. These patients are not only extremely sensitive to the suns radiation but, unlike the majority of psoriatic patients who tend to find the sun therapeutic and spend a long periods of time outdoors or on sunbeds, they generally choose not to go outside and as a result their skin is extremely sensitive and prone to erythema. Patients of skin type 4 included those who were naturally extremely pigmented but in certain cases it was also obvious that their skin had become thickened and very pigmented due to continuous exposure over the years in a personal effort to treat themselves with sun or artificial radiation. Thus, the skin would already be adapted to a certain degree before the initial treatment and higher radiation levels were required to produce an effect at the base of the epidermis. So although there is a maximum dose of radiation which would generally be exceeded in phototherapy additional natural exposure is unknown. Patients who undergo radiation treatment of this type should therefore be warned about the dangers of exposure to radiation generally (e.g. carcinoma, melanoma etc.) as well as the added risks through treatment.

The patients who participated in this study probably will probably be representative of the population presenting in dermatology clinic throughout Britain and therefore the results of this study have a potential for the improving narrowband UVB protocols. Having analysed the data it has been found that

the rate of skin adaptation does not depend upon skin type and there is a significant pattern to tolerance development emerging. There is adaptation deviations and following 15 treatments the amount of adaptation varies from 1.2 - 2.55. Deviations will be due to differences in cumulative doses, the differences in treatment numbers per week, inaccuracies in reading MEDs, and previous personal radiation exposures. Missing one or two treatments has not been found to be significant

5.4 Improving the Study

More consistent results could have been acquired if I was able to ensure that I was available to read every MED. The perception of erythema varies from one person to another and therefore anomalies are inevitable if a different individual is recording the results.

If all patients attended the same number of treatments each week this too could have improved accuracy, although the results do not find the differences in adaptation between those receiving treatment twice a week and those attending three times significantly different on average. Therefore, for the sake of the study if the number of treatments per week was kept constant it would mean that changes in tolerance resulting from missed treatments could be pinpointed more accurately and adaptation changes due to skin types may be more evident.

If the phototest equipment was more portable and able to be strapped to the patients body during testing this would improve the test enormously because a lot of patients found it very difficult to maintain the same position for the period of time required (approximately 8 and 16 minutes). Often, particularly during the high dose ($3J/cm^2$) exposure, patients would move their arm and the results became less reliable. The problem of people not holding their arm close enough to the machine also arose and straps would have ensured patients were positioned correctly for each test. Also, if the radiation could have been given over a shorter period of time this would have improved the accuracy of

the test by reducing the potential time that the patient is irradiated and therefore reducing the time available for movement.

Patients who are exceptionally hairy should have had the hair removed because hair attenuates UV radiation to some extent thus making the patient seem more tolerant to the radiation than they actually are. The hair would have to be gently removed with scissors and not a razor, however, because shaving removes the top layer of dead epidermal cells, exposing the lower, more sensitive layers (for this reason shaving the patient is often used in departments such as ECG in order to produce a good electrical contact).

The phototests were performed on the upper part of the arm because it was thought that this area is less likely to have been exposed to sunlight, even in the summer T-shirts cover the upper arm. However, in psoriatic patients, who generally improve in the summer, exposure of as much of the skin as possible tends to be the norm and the upper arm is therefore more tolerant than the stomach or buttocks. This alters the results because it means that the skin tested is more tolerant than was originally thought, but other areas of the patient are not as well adapted. This was considered in producing an alternative regimen in order to prevent the more sensitive skin of the torso becoming overexposed and excessively erythemal. In order to improve the adaptation data it might be more desirable to irradiate the skin of the inner aspect of the arm, the buttock, back or chest. It is important to use the least tolerable area of the body because these are the areas that become erythemal first and therefore it is these areas that prevent higher doses of radiation from being administered. It must be remembered that skin from different areas of the body have different thickness (see chapter 1) and therefore different parts of the body will react differently to radiation. For these reasons a series of simultaneous light tests on different parts of the body should have been performed so that a regimen that is related the entire body can be produced. It is the entire body that is to be treated after all.

If the study was to be repeated the above point would be considered and several other alterations would be made. The opening times of the department

were 9:00am to midday and 1:00 to 7:00pm. This often proved difficult because I was only present in the department from 1:00 to 5:00pm. The majority of patients visited the department at similar times each week but attendance is at the patients convenience, which sometimes proved difficult to me because it meant I could not perform a phototest or personally read the patients' results. Therefore, upon repeating the study I would ensure I was available during all opening hours to carry out the phototests.

The study was performed over a period of 1 year. During this time the department closed for holidays and patients had to reschedule appointments. However, this was difficult to fit into the mathematical equation because the equation is based upon being treated at regular intervals. If the study was to be repeated the results would be easier interpreted if the patients were advised to miss treatments instead of rescheduling them for an alternative day and this could then be easily analysed once the course is completed.

5.5 Conclusion.

The majority of studies that have been performed in the past used broadband UVB as their basis e.g. Young 1972, Anderson 1984. This study was aimed at collecting data that enabled a more efficient protocol to be produced for narrowband UVB, a protocol with reduced carcinogenicity and maximum efficiency. The data were collected over a period of 1 year to enable a wide range of patients to be tested and to produce a large pool of data. The data were analysed and a mathematical model was derived. The determinants for the model were not found to include skin type, sex or age and it was also established that missing 1 treatment (up to 7 days) did not significantly alter tolerance development. Therefore, there was no need to alter a patient's regime if he/she did not attend one treatment or cancelled an appointment.

The study indicates that it is possible to significantly reduce the intensity of UVB radiation for each treatment course and only reduce the effectiveness slightly ($P= 0.02$). Pre- and post-treatment scores actually showed very little improvement in disease severity with the original protocol and no improvement

with the modified protocol. The possibility of reducing radiation doses when using narrow band UVB is because narrow band UVB is much more intense in its healing effect than broadband UVB. The fact that narrowband UVB produces erythema at smaller increments than broadband UVB indicates the reason why a significantly higher number of patients become burnt during the treatment course (28% green patient and 5% yellow patients). Through reducing the radiation dose, the revised protocol enables an efficient level of treatment to be delivered to patients without overexposure, thus keeping the amount of radiation to a minimum and therefore reducing the probability of carcinogenesis.

The revised protocol was not significantly different in the number of weeks before treatment clearance, the top row dose or the number of treatment sessions during the course.

Therefore, the mathematical model has enabled a protocol to be produced which has an improved safety profile: reduced potential for episodes of burning and reduced cumulative doses of UVB but the effectiveness of treatment was slightly reduced and questions concerning its efficiency should be answered prior to general adoption of the protocol for patient use. It may also be worthwhile following up this study by comparing the length of time the green and yellow patients remain in remission as this must also be considered in deciding if the 'new' protocol is a success. The conclusions drawn from this study also reflect the conclusions of Hofer et al (1998) and George at al (1998) who also performed high/low comparative studies and by pooling my results with those of Hofer and George further evidence is provided that suggests the lower dose regimen, which is less carcinogenic, would be more appropriate.

Appendix 1

Phototherapy Treatment Regimen Tables

Begin treatment course with a dose of 0.3 J/cm². Move across the first row until redness is seen 24 hours after exposure. If the redness is equivocal (ie barely perceptible) give dose in row immediately below. If a definite redness is seen, give dose in row diagonally to left. Aim to keep in this column but move diagonally downwards left or right to reduce or accelerate treatment, respectively. Circle each dose that is given. Tick (✓) skin condition and redness columns appropriately each time patient attends for treatment. Write any relevant comments following exposure overpage.

Name:			Date								
			sig'd								
℞ No.	Date	sig'd	Skin condition				Dose J/cm²	0.3 → ↙ ↓	no redness	0.5 → ↙ ↓	no redness	0.7 → ↙ ↓	no redness	→ 0.9 ↙ ↓	Is skin red today (Y/N)?
			↓	=	↑	☺		definite redness	equivocal redness	definite redness	equivocal redness	definite redness	equivocal redness	definite redness	equivocal redness	
								0.1	0.2	0.3	0.4	0.5	0.6	0.6	0.7	
								0.1	0.2	0.3	0.4	0.5	0.6	0.6	0.7	
								0.2	0.3	0.3	0.4	0.5	0.6	0.7	0.8	
								0.2	0.3	0.4	0.5	0.6	0.7	0.7	0.9	
								0.2	0.3	0.4	0.5	0.6	0.7	0.7	0.9	
								0.2	0.3	0.4	0.5	0.6	0.8	0.9	1.0	
								0.2	0.3	0.4	0.6	0.7	0.8	0.9	1.0	
								0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.1	
								0.3	0.4	0.5	0.6	0.7	0.9	1.0	1.1	
								0.3	0.4	0.5	0.6	0.8	0.9	1.0	1.2	
								0.3	0.4	0.5	0.7	0.8	0.9	1.1	1.2	
								0.3	0.4	0.5	0.7	0.8	1.0	1.1	1.2	
								0.3	0.4	0.5	0.7	0.8	1.0	1.1	1.3	
								0.3	0.4	0.6	0.7	0.9	1.0	1.2	1.3	
								0.3	0.4	0.6	0.7	0.9	1.0	1.2	1.3	
								0.3	0.5	0.6	0.8	0.9	1.1	1.2	1.4	
								0.3	0.5	0.6	0.8	0.9	1.1	1.2	1.4	
								0.3	0.5	0.6	0.8	0.9	1.1	1.3	1.4	
								0.3	0.5	0.6	0.8	1.0	1.1	1.3	1.5	
								0.3	0.5	0.6	0.8	1.0	1.2	1.3	1.5	
								0.4	0.5	0.6	0.8	1.0	1.2	1.3	1.5	
								0.4	0.5	0.7	0.8	1.0	1.2	1.3	1.5	
								0.4	0.5	0.7	0.9	1.0	1.2	1.4	1.5	

Key: ↓ worse; = no change; ↑ improved; ☺ clear

Cumulative dose.....J/cm² Total no. treatment sessions:.....

Begin treatment course with a dose of 0.3 J/cm². Move across the first row until redness is seen 24 *hours after exposure. If the redness is equivocal (ie barely perceptible) give dose in row immediately below. If a definite redness is seen, give dose in row diagonally to left.* ***Aim to keep in this column but*** *move diagonally downwards left or right to reduce or accelerate treatment, respectively. Circle each dose that is given. Tick (✓)* ***skin condition*** *and* ***redness*** *columns appropriately each time patient attends for treatment. Write any relevant comments following exposure overpage.*

Name:							Date								
							sig'd								
℞ No.	Date	sig'd	Skin condition				Dose J/cm²	0.3 → ↙ ↓	no redness	0.5 → ↙ ↓	no redness	0.7 → ↙ ↓	no redness	→ 0.9 ↙ ↓	Is skin red today (Y/N)?
			↓	=	↑	☺		definite redness	equivocal redness	definite redness	equivocal redness	definite redness	equivocal redness	definite redness	equivocal redness	
								0.1	0.2	0.2	0.3	0.4	0.5	0.6	0.6	
								0.2	0.2	0.3	0.4	0.5	0.7	0.7	0.8	
								0.2	0.3	0.4	0.5	0.6	0.8	0.9	1.0	
								0.3	0.4	0.5	0.6	0.8	1.0	1.1	1.2	
								0.3	0.4	0.6	0.7	0.9	1.2	1.3	1.5	
								0.4	0.5	0.7	0.9	1.1	1.4	1.5	1.7	
								0.4	0.6	0.8	1.0	1.2	1.6	1.7	2.0	
								0.5	0.7	0.9	1.1	1.4	1.8	2.0	2.2	
								0.5	0.7	1.0	1.2	1.6	2.0	2.2	2.5	
								0.6	0.8	1.1	1.4	1.7	2.2	2.5	2.7	
								0.6	0.9	1.2	1.5	1.9	2.4	2.7	3.0	
								0.7	1.0	1.3	1.6	2.1	2.6	2.9	3.3	
								0.7	1.1	1.4	1.8	2.2	2.8	3.1	3.5	
								0.8	1.1	1.4	1.9	2.4	3.0	3.3	3.7	
								0.8	1.2	1.5	2.0	2.5	3.2	3.5	4.0	
								0.9	1.3	1.6	2.1	2.6	3.3	3.6	4.2	
								0.9	1.3	1.7	2.2	2.7	3.4	3.7	4.4	
								1.0	1.4	1.7	2.3	2.8	3.5	3.8	4.5	
								1.0	1.5	1.8	2.4	2.9	3.6	3.9	4.6	
								1.1	1.5	1.9	2.4	3.0	3.7	4.0	4.7	
								1.1	1.6	1.9	2.5	3.1	3.8	4.1	4.8	
								1.2	1.6	2.0	2.5	3.1	3.9	4.2	4.9	
								1.2	1.7	2.0	2.6	3.2	4.0	4.3	5.0	

Key: ↓ worse; = no change; ↑ improved; ☺ clear

BL Diffey/2 days per week/Revised July 1997

Cumulative dose.....J/cm² Total no. treatment sessions:.....

*Begin treatment course with a dose of 0.3 J/cm². Move across the first row until redness is seen 24 hours after exposure. If the redness is equivocal (ie barely perceptible) give dose in row immediately below. If a definite redness is seen, give dose in row diagonally to left. Aim to keep in this column but move diagonally downwards left or right to reduce or accelerate treatment, respectively. Circle each dose that is given. Tick (✓) **skin condition** column appropriately each time patient attends for treatment. Write any relevant comments following exposure overpage.*

Date															
sig'd															
Date	sig'd	Skin condition				Dose J/cm²	0.3 → ✓↓	no redness	0.5 → ✓↓	no redness	0.8 → ✓↓	no redness	→ 1 ✓↓	other exposure J/cm²
		↓	=	↑	☺		definite redness	equivocal redness	definite redness	equivocal redness	definite redness	equivocal redness	definite redness	equivocal redness	
						0.2	0.2	0.3	0.4	0.5	0.6	0.7	0.8		
						0.2	0.3	0.3	0.4	0.5	0.7	0.8	0.9		
						0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9		
						0.2	0.3	0.4	0.5	0.6	0.8	0.9	1.0		
						0.2	0.3	0.4	0.6	0.7	0.9	1.0	1.1		
						0.3	0.4	0.5	0.6	0.8	1.0	1.1	1.2		
						0.3	0.4	0.5	0.6	0.8	1.0	1.2	1.3		
						0.3	0.4	0.5	0.7	0.9	1.1	1.2	1.4		
						0.3	0.4	0.6	0.7	0.9	1.2	1.3	1.5		
						0.3	0.5	0.6	0.8	1.0	1.3	1.4	1.6		
						0.4	0.5	0.7	0.9	1.1	1.4	1.5	1.7		
						0.4	0.6	0.7	0.9	1.2	1.5	1.6	1.8		
						0.4	0.6	0.8	1.0	1.2	1.6	1.7	2.0		
						0.4	0.6	0.8	1.0	1.3	1.7	1.9	2.1		
						0.5	0.7	0.9	1.1	1.4	1.8	2.0	2.2		
						0.5	0.7	0.9	1.2	1.5	1.9	2.1	2.3		
						0.5	0.7	1.0	1.2	1.6	2.0	2.2	2.5		
						0.6	0.8	1.0	1.3	1.6	2.1	2.3	2.6		
						0.6	0.8	1.1	1.4	1.7	2.2	2.4	2.7		
						0.6	0.9	1.1	1.4	1.8	2.3	2.6	2.9		
						0.6	0.9	1.2	1.5	1.9	2.4	2.7	3.0		
						0.7	0.9	1.2	1.6	2.0	2.5	2.8	3.2		
						0.7	1.0	1.3	1.7	2.1	2.6	3.0	3.3		
						0.7	1.0	1.3	1.7	2.2	2.8	3.1	3.5		
						0.8	1.1	1.4	1.8	2.3	2.9	3.2	3.6		
						0.8	1.1	1.5	1.9	2.4	3.0	3.4	3.7		
						0.8	1.2	1.5	1.9	2.5	3.1	3.5	3.9		
						0.9	1.2	1.6	2.0	2.6	3.2	3.6	4.0		
						0.9	1.3	1.6	2.1	2.7	3.4	3.7	4.2		
						0.9	1.3	1.7	2.2	2.7	3.5	3.9	4.3		
						1.0	1.3	1.7	2.2	2.8	3.6	4.0	4.5		
						1.0	1.4	1.8	2.3	2.9	3.7	4.1	4.6		
						1.0	1.4	1.9	2.4	3.0	3.8	4.3	4.8		
						1.0	1.5	1.9	2.5	3.1	3.9	4.4	4.9		

Key: ↓ worse; = no change; ↑ improved; ☺ clear

Appendix 2

Phototest Exposure Record Charts

TL01 Phototesting Record Sheet

Record No:.....

Patient Name:..... Frequency: 2 / 3 times per week

Sex: M / F Age:..... Medication: Yes / No

Setting dose range

If previous dose range was *low* and 3 or more sites showed erythema on last phototest, keep dose range set to *low*;
OR if previous dose range was *low* and only 1 or 2 sites showed erythema on last phototest, set dose range to *high*;
OR if previous dose range was *high,* keep dose range set to *high*.
Aim to phototest patients on alternate attendances, and on the left and right arm, alternately.

First attendance (pre-treatment MED)

Date of last treatment: n/a	Treatments so far: 0	Date today:
Dose range: *low / high*	Arm: *left / right*	Cumulative dose J/cm² 0
Date MED read:	MED read by:	

MED: Mark a cross (×) in the appropriate box

highest dose	1	2	3	4	5	6	7	8	9	10	*lowest dose*

Phototest: 2

Date of last treatment:	Treatments so far:	Date today:
Dose range: *low / high*	Arm: *left / right*	Cumulative dose J/cm²
Date MED read:	MED read by:	

MED: Mark a cross (×) in the appropriate box

highest dose	1	2	3	4	5	6	7	8	9	10	*lowest dose*

Phototest: 3

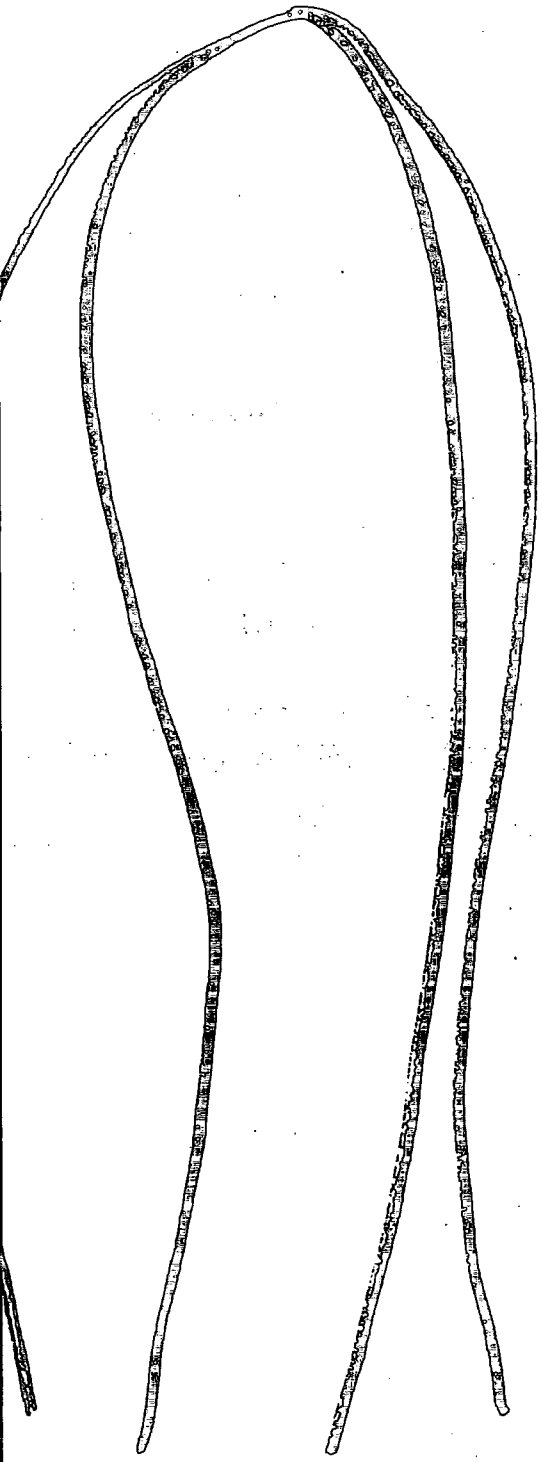
Date of last treatment:	Treatments so far:	Date today:
Dose range: *low / high*	Arm: *left / right*	Cumulative dose J/cm²
Date MED read:	MED read by:	

MED: Mark a cross (×) in the appropriate box

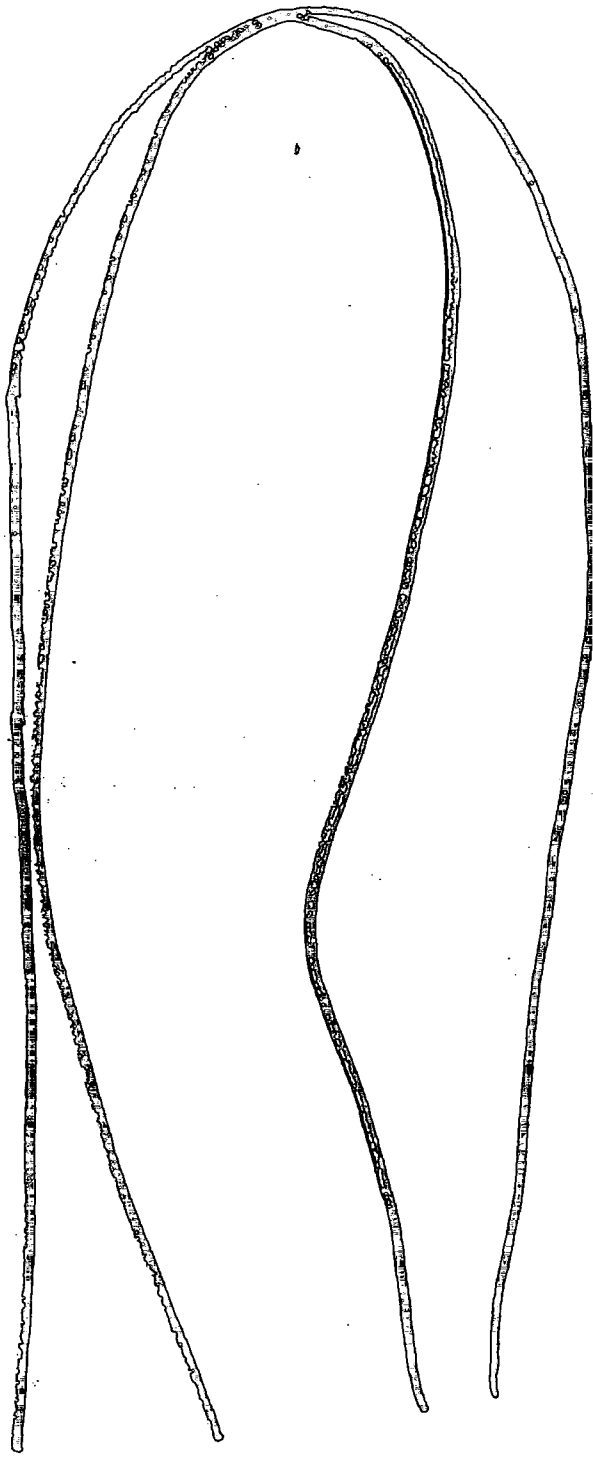
highest dose	1	2	3	4	5	6	7	8	9	10	*lowest dose*

Patient's name :

LEFT ARM



RIGHT ARM



REFERENCES

Abel E.A., DiCicco L.M., Orenberg E.K. et al 1986. Drugd in Exacerbation of Psoriasis. Journal of the American Academy of Dermatology. 15. 1007-22.

Anderson T.F., Thomas P., Waldinger M.D., Voorheesm D. 1984. UVB Phototherapy, An Overview. Archives of Dermatology. 120: 1502-1507.

Axmann D. 1918. Behandlung der Pigmentatrophe mittels Lichtsensibilisierender Stoffe. Munch Med. Wschr. 65: 45.

Barth J.H., Baker H. 1986. Generalized Pustular Psoriasis (precipitated by trazodone) in the Treatment of Depression. British Journal of Dermatology. 115 629-30.

Bauer F. 1986. Cell Kinetics. In Mier P.D. , van der Karkhof. Textbook of Psoriasis. Edinburgh Churchhill livingstone. 100-112.

Baughman R., Sobel R. 1971. Psoriasis, Stress and Strain. Archives of Dermatology. (103) 599-605.

Berne R.M., Levy M.N. 1990. Principles of Physiology. Wolfe Publishers Limited.

Bos J.D. 1988. The Pathomechanisms of Psoriasis: the Skin, Immune system and Cyclosporin , British Journal of dermatology. 118 141-55.

Braverman I.M., Fanferko I.E. 1982. Studies in Cutaneous Aging: The Elastic Fibre Network. Journal of Investigative Dermatology. 82 (78): 434-443.

Buchheri L., Katchen B.R., Karter A.J., Cohen S.R. 1997. Acitretin Therapy is effective for Phototherapy Accociated with Human Immunodeficiency Virus Infection. 133(6): 711-715.

Cox N., Farr P., Diffey B.L. 1989. A Comparison of the Dose Response Relationship for Psoralen UVA Erythema and UVB Erythema. Archives of Dermatology. 125: 1653-1657.

Dale B.A., Holbrook K.A., Steinert P.M. 1978. Assembly of Sratum Corneum; Basic Protein and Keratin Filament into Macrofibrils. Nature. 276:729-731.

Dave V.K.. 1997. Smoking and Immunology in: Skin Care. Class Publishing.

Diffey B.L. 1982. Ultraviolet Radiation in Medicine. Adam Hilger, Bristol.

Diffey B.L., McKinlay A.F., 1983. The UVB Content of UVA Fluorescent Lamps and its Erythemal Effectiveness in Human Skin. Physics in Medicine and Biology. 28: 351-358.

Diffey B., Farr P., Ibbotson S.H. 1996. The Effect of Topical Indomethacin on UVR induced Erythema. British Journal of Dermatology. 96 (135): 525-527.

Dover R., Watt F.M. 1987. Measurement of the Rate of Epidermal Differentiation-Expression of Involverin by s-phase Keratinocytes in Culture and Psoriatic Plaques. Journal of Investigative Dermatology. 89: 349-352.

Duller P., van Veen-Viebor M. 1986. Psychosocial Aspects . In: Mier P.D., van der Kerkhof PCM eds. Textbook of Psoriasis. Edinburgh Churchill Livingstone. 84-95.

Dunna S.F., Findlay A.Y.. 1989. Psoriasis: Improvement during and Worsening After Pregnancy. British Journal of Dermatology. 120. 584.

Epstein E. 1947. Photosensitisation in the Treatment of Psoriasis. British Medical Journal. 8203-8207.

Ebling, Wilkinson, Rock. 1992. Textbook of Dermatology. Volume 4. Blackwell Scientific Publications.

Ellis C.C., Wooldridge W.E., Weiss R.S. 1948. The Treatment of Psoriasis with Liquid Carbonis Detergins. Journal of Investigative Dermatology. 10: 455-459.
Marcel Dekker. 105-116.

El Mofty A.M. A Preliminary Clinical Report on the Leucodermia with *Amni majus.* Journal of the Egypt Medical Association. 31: 651-665.

Eyre R.W. Kreuger C.G. 1984. The Koebner Response in Psoriasis. In :
Roenigk H. H., Maibach H.I. eds. Psoriasis. New York:

Faber E. M., Nall L. 1968. Psoriasis: A Questionnaire of 2144 Patients. Archives of Dermatology 18:248.

Fischer T. 1976. Ultraviolet Light Treatment of Psoriasis. Acta Derm Venereol. 56: 473-479.

Flindt-Hanson H., McFadden N., Eeg-Larson T., Thune P. 1991. Effect of a new Narrow Band UVB Lamp on Photocarcinogenesis in Mice. 71: 245-248.

Gatson L., Lasonde M. Bernier-Buzzanga J. et al. 1897. Journal of American Acadamy of Dermatology. 17 82-86.

Gibbs N.K., Trayner N.J., Mackie R.M., Cambell I., Johnson B.E., Fergusen J. 1995. The Photohemorigenic Potential of Broad Band (170-350nM) Phototherapy and Narrow Band (311-313 nM) Phototherapy Scources Cannot be Predicted by their Edematogenic Potential in Hairless Mouse Skin. Journal of Investigative Dermatology. 104: 359-363.

Gilmour J.W., Vestey J.P., George S., Naval M. 1993. The Effect of Phototherapy and Urocanic Acid on Natural Killer Cell Function. Journal of Investigative Dermatology. 101 (93): 169-174.

Ginsburg M.D., Iona H. 1995. Psychological and Phychophysiological affects of Psoriasis. Cells.13(4): 95.

Goekerman W.H. 1925. Treatment of Psoriasis. North West Medicine. 24: 229-231.

Gonzalez S., Hegyi V., Baqer A., Sadiq I., Kollias N. 1996. Development of Cutaneous Tolerance to Ultraviolet B during Phototherapy for Psoriasis. Photodermalology, Photoimmunology and Photomedicine.12: 73-78.

Green C., Ferguson J., Lanshmiphathi T. and Johnson B.E. 1988. 311 UV Phototherapy-an Effective Treatment for Psoriasis. Philips Lighting. Product information.

Grupper C. 1980. Psoriasis. Proceedings International Symposium on Psoriasis. Stanford, California. Stanford University Press.

Gupta M.A., Schork N.J.,Ellis C.N. 1993. Alcohol Intake and Treatment Responsiveness of Psoriasis. Journal of the American Acadamy of Dermatology. 28: 730-732.

Halprin K.M., Adachi K., Yoshikawa K. et al 1975. CAMP and Psoriasis. Journal of Investigative Dermatology. 65. 170-178.

Harber L.C., Bickers D.R., Epstein J.H. et.al. 1974. Report on UV Light Sources. Archives of Dermatology. 109: 833-839.

Henseler T., Christophers E., Honigsmann H., Wolf K. 1987. Skin Tumours in the European PUVA Study. Journal of the American Academy of Dermatology. 16: 108-116.

Hughes S.P.F.,Benson M.K.D.A., Colton C.L. 1987. Orthopaedics. The Principles and Practice of Musculoskeletal Surgery. Church Livingstone UK Ltd. Longman Group.

Hunter J.A.A., Savin J.A., Dahl M.V. 1995. Clinical Dermatology. 2nd Edition Blackwell Science.

Horwitz S.N., Frost S. A Phototherapy Cabinet for Ultraviolet Radiation Therapy 1981. Archives of Dermatology. 117: 469-473.

Ingram J.T. 1954. The Significance and Managemant of Psoriasis. British Medical Journal. ii 823-8.

Ingram J.T. The Approach to Psoriasis. British Medical Journal. 11: 591-594.

Karvonen J., Kokkonen Ruotsalainen E. 1989. 311nm UVB Lamps in the Treatment of Psoriasis with the Ingram Regimen. Acta Derm Venereol. 69: 82-85.

Kreuger J.G., Wolfe J.T., Tsukifuji Nabeya R., Vallet V.P., Gilleaudeau P., Heftler N.S., Austin L.M., Gottlieb A.B. 1995. Successful Ultraviolet B Treatment of Psoriasis is Accompanied by a Reversal of Keratinocyte Pathology and by Selective Depletion of Intraepidermal T cells. Journal of Experimental Medicine.182: 2057-2068.

Larko O. 1982. Phototherapy of Psoriasis: Clinical Aspects and Risk Evaluation. Acta Derm Vehereol. Suppl. 103: 1-24.

Lee R.E., Gaspari A.A., Lotze M.T. et al 1988. Interleukin 2 and Psoriasis. Archives of Dermatology. 124 1811-15.

Stern R.S., Zeirler S., Parrish J.A. 1980. Skin Carcinoma in Patients with Psoriasis Treated with Topical Tar and Artificial Radiation. Lancet 732-735.

Marcelo C.L., Duel E. A. Stawiski M. A. et al. 1979. Nucleotide levels in Psoriatic Skin and Normal Keratinized Lesions. Journal of Investigative Dermatology. 72 20-4.

Marks R. 1996. Control of Melanoma : The Public Health Approach. C.A. Cancer Journal Clin. 46(4): 199-216.

Monk B.E., Neill S.M. 1986. Alcohol Consumption and Psoriasis. Dermatologica. 173 57-60.

Nanney L.B. et al 1986. Altered [I^{125}] , Epidermal growth Factor binding and Receptor Distribution in Psoriasis.Journal og Investigative Dermatology. 86 260-65.

Nickeloff B.J. 1988. Role of Interferon Gamma in Cutaneous Trafficking of Lymphocytes with Emphasis on Molecular and Cellular Adhesion Events. Archives of Dermatology. 124 1835-43.

Ockenfels H.M., Wagner S.N., Oeljeklaus P., Schneck B., NuBbaum G., et al. 1996. Inhibition of T Cell cAMP Formation by Cyclosporin A and FK506. Naunyn-Schmiedeberg's Archives of Pharmacology. 96(353): 513-513.

Ortonne J. 1996. Pigmentary Disorders Associated with Sun Exposure. Journal of Dermatology Treatment. 7(2): 57-58.

Parrish J.A., Fitzpatrick T.B., Tanenbaum L., Pathak M.A. 1974. Photchemotherapy of Psoriasis with Oral Methoxalen and Longwave Ultraviolet Light. New England Journal of Medicine.29: 1207-1211.

Parrish J.A. 1977. The Treatment of Psoriasis with Ultraviolet Light (UVA). Archives of Dermatology. 113: 1525-1528.

Parrish J.A., Jaenicne K.F. 1981. Action Spectrum for Phototherapy of Psoriasis. Journal of Investigative Dermatology. 76: 359.

Picot E., Meunier L., Picot-Debeze M.C. et al. 1992. Treatment of Psoriasis with a 311nm UVB Lamp. British Journal of Dermatology. 92 (127): 509-512.

Rampen F.H.J., Fleuren B.A.M., de Boo T.M., Wim A., Lemmers A.U.G. 1988. Unreliability of Self Reported Burning and Tanning Ability. Archives of Dermatology. 124: 885-888.

Reaven E.P., Cox, A.J. 1965. Histadine and Keratinization. Journal of Investigative Dermatology. 45: 422-431.

Ros A-M., Eklund G. 1987. Photosensitive Psoriasis. Journal of the American Academy of Dermatology. 17. 752-8.

Rosenberg E.W., Noah P.W., Zanalli M,D., et al. 1986. Use of Rifampicin with Penicillin and Erythromycin in the Treatment of Psoriasis. Journal of the American Academy of Dermatology. (14) 761-764.

Schafetter-Kochanck K., Walschek M., Bolsen K. et. al. 1992. The Environmental Threat To Skin. Martin Dunitz Publishers. London.

Simon M., Green, H. 1987. Participation of Membrane Associated Proteins in the Cross Linking of Involucrin. 36: 827-834.

Stern R. 1990. Genital Tumers Among Men with Psoriasis Exposed to Psoralens and UVA Radiation and UVB Radiation. New England Journal of Medicine. 322: 1093-1097.

Stern R.S., Thibodeau L.A., Kleinerman R.A. et.al. 1979. Risks of Cutaneous Carcinoma in Patients Treated with Oral Methoxsalen Photochemotherapy for psoriasis. New England Journal of Medicine 306: 800-813.

Tomfohrde J., Silverman A., Barnes R., Fernandez-Vina M.A., Young M., Lory D., Morris L., Wuepper K.D., Stastney P. Menter A. et al. 1994. Gene for

Familial Psoriasis Suceptability Mapped to the Distal End of Chromosome 17q. Science 264(5162): 1141-1145.

Tournier S., Gerbaud P., Anderson W.B., Lohman S.M., Evian-Brion D., Raynand F. 1995. Post Translational Abnormalities of the Type 11 Cyclic AMP-Dependent Protein Kinase in Psoriasis Modulation by Retinoic Acid. Journal of Cellular Biochemistry. 57: 647-654.

Van Weelden H., Van der Leun, J.C., 1986. UVB Phototherapy: Principles, Radiation Sources, Regimens. Current Problems in Dermatology. 15: 39.

Van Weelden H., De La Faille B.H., Young E., Van der Leun J.C. 1988. A New Development in UVB Phototherapy of Psoriasis. British Journal of Dermatology. 119: 11-19.

Van Weelden H., Van der Leun J.C. 1984. Improving the Effectiveness of Phototherapy for Psoriasis. British Journal of Dermatology. 11: 484.

Van Weelden H., Young E., Van der Leun J.C. 1980. Therapy of psoriasis: Comparison of Photochemotherapy and Several Variants of Phototherapy. British Journal of Dermatology. 103: 1.

Watson W., Cann H.M., Farber E.M. et.al. 1972. The Genetics of Psoriasis. Archives of Dermatology. 105: 197-207.

Whyte H.J., Baigham R.D. 1964. Acute Guttate Psoriasis and Streptococcal Infection. Archives of Dermatology.89: 350-356.

Wulf H.C., Hansen N., Bech-Thomsen, N. 1994. Differences in Narrow Band UVB and Broad Band UVB Photocarcinogeneses in Lightly Pigmented Hairless Mice. 10: 192-197.

Young E. 1970. The External Treatment of Psoriasis: A Controlled Investigation of the Effects of Dithranol. British Journal of Dermatology. 82: 516.

Young E. 1970. The External Treatment of Psoriasis: a Controlled Investigation of the Effects of Coal Tar. British Journal of Dermatology. 82: 510.

Young E. 1972. UV Therapy of Psoriasis: a Critical Study. British Journal of Dermatology. 87: 379-382.

Young E. 1990. Photocarcinogenicity of Psoriasis used in PUVA Treatment. Present status in Mouse and Men. Journal of Photochemistry and Photobiology. 6 (1-2): 237-247.